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## OBSERVATIONS ON THE CONDITION OF THE SPLEEN AND LEUCOCYTES IN 'TRENCH FEVER'

BY D. L. TATE AND J. W. MCLEOD

At the present time, when a number of careful and detailed accounts of the clinical features of the disease which has come to be known as 'trench fever' have already appeared, it would be superfluous to write another. It is therefore understood that, in this paper, by 'trench fever' is meant the condition which has already been described with very little divergence by Hunt and Rankin (1) (1915), McNee, Renshaw, and Brunt (2) (1916), Hurst (3) (1917), Herringham (4) (1916), and recently in an official memorandum by Balfour (5). We may proceed then without any further discussion to the two points in connexion with this disease in which our observations differ from and add to those already published. These are the questions of splenic enlargement and of the modifications in the number and type of the circulating leucocytes in the course of the disease.

### *Splenic Enlargement in 'Trench Fever'.*

Of the papers dealing with this disease to which we have had access the greater number either make no mention of the spleen or say definitely that it is not enlarged. Thus Hunt and Rankin (1), and later Herringham (4), say that the spleen is not enlarged; whereas McNee, Renshaw, and Brunt (2), Coombs (6) (1917), and Balfour (5) describe the disease without mentioning the condition of the spleen. Neither is any mention of it made by Chambers (7) (1917) in the paper on infective fibrositis in which he describes a disease with febrile onset and a marked tendency to localization of pains in the shins. Houston and McCloy (8) (1916), in an article entitled 'The Enterococcus in Trench Fever', describe three types. The first of these they call a septicæmic type; it is characterized by continuous fever for ten days or longer, and is associated with splenic enlargement. Their two other types are 'trench fever' proper and 'myalgia', and in these they do not mention splenic enlargement. Since the first type described by these authors does not correspond to 'trench fever' in the sense now generally accepted, it may be said that they do not describe the occurrence of splenic enlargement in that condition. In a short paper on this subject Davies and Weldon (9) (1917) make the following non-

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committal statement: 'The spleen is certainly not usually enlarged either to percussion or to palpation.' There is, however, one definite record of the observation of splenic enlargement in this condition, that of Hurst (3), who says, 'In the first attack the spleen is sometimes palpable and is found to be enlarged on percussion, and there may be some tenderness in the left hypochondrium'. Hurst assumes, however, that this may be a feature of the disease peculiar to the East since his observations had been made there and were different from those which had been recorded previously in France.

It is one of the objects of this paper to state that, in working over an area of twenty or thirty miles with the B. E. F., it has been our experience as well as that of most clinical observers that we have met, especially Capt. R. C. Clarke, R.A.M.C., that a moderate degree of splenic enlargement is a fairly frequent characteristic of this disease either in the initial attack or in the earlier relapses. Attention to this fact was first drawn for one of us (J. W. M.) by frequent requests to examine cases of short fever with enlarged spleen in order to get bacteriological evidence of paratyphoid infection. These examinations gave negative results, and apart from the splenic enlargement there was little about these cases to suggest paratyphoid infection, since the outstanding features in most were a short and irregular pyrexia with complaint of pains all over the body, complete absence of catarrhal symptoms, and in many cases one or more febrile relapses. From May 1916 till the end of the summer an endeavour was made to see as far as possible all cases of pyrexia of unknown origin which were admitted to the C. C. S.'s in the immediate neighbourhood of the laboratory. The object was to make sure that no case which might be one of paratyphoid infection should escape bacteriological examination. Amongst those treated as suspect were any cases in which fever was associated with splenic enlargement. It was not possible to have a complete record of the course of the fever in many of those cases owing to the rapidity with which they were evacuated, but a short note was made of the outstanding clinical features of every case in which a bacteriological examination for bacilli of the enteric group was made. A survey of these records shows that, when all cases of fever in which some evidence of catarrh or other focal lesion capable of explaining the pyrexia are excluded, there remained a total of 107 cases in which bacteriological examination for bacilli of the enteric group was negative. In twenty-one of these the spleen was definitely palpable, i.e. in 19.6 per cent.

Paratyphoid, which does not appear to be endemic in the area, had been fairly common in the earlier part of the year amongst a body of troops which had returned infected from the Eastern theatre, but had rapidly diminished as the summer opened. In the clearing stations concerned during the period for which these observations are recorded there were only six cases of paratyphoid fever in which bacilli were isolated from the patients. These six cases showed continued fever while under observation; all had heavily furred or dry tongues and were distinguished by one or more of the following symptoms: abdominal pain, diarrhoea, an area of pulmonary consolidation, or rose spots. Such features

were not met with in the 107 cases mentioned above, and amongst these heavy furring of the tongue was exceptional. Two of the paratyphoid cases had palpable spleens, in two the spleen could not be palpated, and for the remaining two palpation was so difficult on account of abdominal pain that the condition of the spleen could not be certainly determined.

In August, 1916, one of us (D. L. T.) made careful observations of eighty cases of P. U. O. admitted to field ambulances from one division. No full record was kept, but they were all cases of short fever with a definite relapse or repeated relapses, and their other clinical features were those which we associate with the disease called 'trench fever'. In addition seven of them had slight diarrhoea of short duration, about twenty-four hours. Eleven of these eighty cases had palpable spleens, i.e. 13.7 per cent.

No bacteriological examination had been asked for as the symptoms had not suggested an infection of the enteric group.

Subsequently a joint investigation of a series of cases from this division was carried out at one of the ambulances with a view to determining some points in connexion with the leucocytic reaction in the disease. As full records were kept the observations as far as they deal with splenic enlargement may be given in detail. In all, twenty-six cases were examined, and in four of these the spleen could be palpated for some time during the illness, i.e. in 15.3 per cent.

The details are as follows:

1. L.-Cpl. B., field ambulance driver. 24.8.16. Sudden onset with fever, severe frontal headache, transient backache, but no definite shivering. Bowels regular, tongue flabby and white. 8.9.16. Nocturnal shin pains and tenderness appeared, and still persisted on 17.9.16 when he was evacuated to a C. C. S.

2. Pte. C., field ambulance bearer. 24.8.16. Sudden onset with shivering which persisted for twelve hours, frontal headache, aching of shoulders and back and front of legs. His complaint was of pain in his bones. The tongue was clean and moist. Shin pains were marked in his relapse.

Blood and stools were examined for bacilli of the enteric group with negative results.

3. Pte. L., T.M. Battery. 31.8.16. Sudden onset with frontal headache and with backache. The tongue was pale and flabby; there was constipation and intense muscular tenderness, especially in his legs, on 3.9.16. He was sent to a convalescent camp on 17.9.16 and transferred to a C. C. S. two days later on account of a relapse.

There was also an examination of the stools and blood in this case with negative results.

4. Pte. M., infantry. 27.8.16. Sudden onset, dizziness, shivering, headache, and general muscular pains. Bowels were regular. 3.9.16. Muscular tenderness marked. 5.9.16. Evacuated to a C. C. S. on account of continued shin pains.

To these may be added a fifth case. This case, which was seen in the field ambulance of another division, was a striking example of the type of 'trench fever' with numerous and marked febrile relapses, and in this case also splenic enlargement was detected by palpation.

The examination of the blood and stools for bacilli of the enteric group gave negative results.

We are indebted to Lt.-Col. Greenlees, D.S.O., R.A.M.C., for the particulars



of this case and for the opportunity of examining it. Unfortunately the chart of this last case was lost; those of the first four are shown.

It is possible that an objection to considering the cases described as instances of 'trench fever' with splenic enlargement may be raised on the score that these were cases of fevers of the enteric group in which the fever was modified on account of typhoid and paratyphoid inoculation. Such a view has been put forward in the discussion of these cases, but it is a very difficult one to accept. An overwhelming majority of them had no clinical resemblance to enteric infections but a very distinct resemblance to 'trench fever'. Further, the fact that in twenty-five consecutive cases of this kind bacteriological examinations gave negative results—in nine cases cultures were made both from blood and stools, in twelve from the blood only, and in four from the stool only—shows that neither a septicaemia nor a definite lesion of the bowel or gall-bladder existed in most of these cases. One expects to fail to isolate bacilli of the enteric group in a certain proportion of infected individuals, perhaps even 50 per cent., but to fail in twelve consecutive examinations means that the bacilli are either absent altogether or present in very small numbers. The violence of the febrile reaction in some of these cases precludes the possibility that they are very mild infections. It seems to us, therefore, to be more reasonable to consider those as cases of 'trench fever' with enlarged spleen until such time as a cryptic form of enteric occurring in inoculated persons, with unusual symptoms and a low infectivity for contacts, shall have been satisfactorily demonstrated.

Taking it then that a palpable spleen was detected in 15 per cent. of the cases of 'trench fever' observed by us, we believe that we are justified in concluding that a moderate degree of splenic enlargement has been a fairly constant, if not invariable, feature of this disease in the district in which our observations have been made.

#### *Study of the Leucocytes in 'Trench Fever'.*

A summary of the opinion in the publications which have dealt with this subject is fairly accurately expressed by saying that a moderate leucytosis, in which the lymphocytes or large hyaline leucocytes are relatively increased, is the rule in the disease.

Hunt and Rankin (1) (1915) made blood examinations in twenty-four cases and got an average leucocytosis of 10,500 with great individual variations ranging from 4,700 to 22,000. They made eleven differential counts and got an average polymorphonuclear count of 58 per cent. with normal numbers of large hyalines and slight relative increase of lymphocytes. They noticed very little variation in the number of leucocytes at varying stages of the disease and with varying degrees of pyrexia.

McNee, Renshaw, and Brunt (2) (1916) give full details of complete blood-counts in ten cases; in two they give differential counts only, and in one they

omit the differential count. Their figure for the average leucocytosis is slightly lower than the foregoing, 9,700, and the variations recorded are less extreme. Their average figure for polymorphs is 66 per cent., that for lymphocytes is 26.3 per cent., and their general conclusion is that there is a slight relative increase of large and small lymphocytes and a rather low figure for large hyaline cells.

Hurst (3) (1917) quotes the figures of the writers mentioned above, but does not give details of his own observations. In one point he is at variance with them, for he alludes to the frequency of a moderate increase of the large hyaline cells and maintains that this, together with other features, suggests a protozoal rather than a bacterial origin for the disease. Balfour's (5) remarks are identical with those of McNee, Renshaw, and Brunt (2). Coombs (6), however, in a careful record of a case with repeated relapses notes a mild polymorphonuclear leucocytosis towards the end of the illness, but as his observations on the blood only relate to one case they have a limited value.

Chambers (7), in the description of the condition which he calls 'trench shin', but which cannot be very clearly differentiated from 'trench fever', says that this condition is associated with a leucytosis in which the polymorphonuclear cells are relatively increased. He only gives details of differential counts in three cases, and the average count of polymorphs for these was 64 per cent. Our own observations with regard to the degree of leucocytosis and its variations are fully in accord with those of Hunt, Rankin, and McNee. Further, our figures for the relative proportions in which the various leucocytes occur differ very little from theirs. We do not believe, however, that these workers are correct in interpreting the results which they record as evidence of the existence of a slight relative lymphocytosis in 'trench fever'. We have not been able to confirm Hurst's (3) observation of a definite increase of the large hyaline cells in this condition.

As our observations are only slightly more extensive than those of the authors just quoted, it is necessary to show some reason why they should be accepted rather than theirs.

There are two respects in which the observations of these, as published, seem to us to have been insufficiently controlled:

1. They do not record a comparison between the patients' differential counts in their convalescent and those in their febrile periods.
2. They do not record any observations of the average differential leucocyte count of healthy men living under the conditions to which their patients had been accustomed.

The advantage of determining the first point is obvious. In support of the second line of control recommended, it may be urged that it is justified in the first place by the usually slight, but in a few instances considerable, variations in the figures quoted by different authorities as 'normal'.

To give four examples (see Table I, p. 10).

Now 30 per cent. of lymphocytes would constitute a slight relative lympho-

cytosis by the three last standards, but not by the first; it is obvious, therefore, that there are factors at play producing a variation in the normal. One of these factors is probably technique; but climate, diet, exposure to vermin, and bacterial inoculations may all play a part, and since the statements which exist as to the influence of these various factors are by no means unanimous, the only satisfactory way of getting a normal standard for comparison is to assess the aggregate influence of the various factors named by taking an average from a number of control observations on healthy individuals living in conditions nearly similar to those which the patients have experienced.

The only attempt which we have noticed to establish data of this kind for the troops is that of Walker, Hall, and Adam (14) (1916). These workers were investigating the differential leucocyte counts of patients convalescent from various infections of the bowel, and they established two normals: one for inoculated and the other for uninoculated men. The number examined in the latter group is not stated, but the average figures given are polymorphs 68 per cent., lymphocytes 23 per cent. In the first group seventy-one men were examined, and the average figures were polymorphs 70.7 per cent., lymphocytes 21.5 per cent.

Our own figures differ considerably from those just quoted, but as Walker, Hall, and Adam's observations were carried out on men in England it is not easy to determine their bearing on the normal amongst soldiers in France.

*Observations of the Average Number and Relative Proportions of the Leucocytes in the Blood of Healthy Soldiers in France.*

The ideal comparison for the observations which we have to record would undoubtedly be a collection of data obtained from men who had been doing regimental work for several months in the trenches in France and who were quite free from any infection of the type which we are discussing. On reflection, however, we concluded that an average normal figure, obtained from individuals of regimental units in which there had been a considerable incidence of 'trench fever', might be erroneous on account of the inclusion of men convalescent from mild infections and others in a condition of latent infection. As far as the question of the total leucocyte count is concerned, this attitude seems to be justified by the publication of Chambers's (7) observation of persistent leucocytosis during long convalescence from the condition which he describes as 'trench shin'.

We have fallen back, therefore, on the plan of arriving at an average normal figure by taking groups of men from different units in which the conditions of life and diet and the degree of exposure to the type of infection under discussion varied considerably, and, lastly, a number of patients with another disease which was likely to be associated with a polymorphonuclear leucocytosis.

Group 1. Men of the R.F.C.; a unit little exposed to the infection under



discussion, and enjoying better conditions as regards diet, &c., than most of the infantry units.

Group 2. Men of a field ambulance; exposure to infection and conditions of life identical with those of 22 per cent. of our patients and somewhat similar to those existing in infantry units.

Group 3. Mixed group, personnel of a field ambulance, of a C. C. S., and of a mobile laboratory. Conditions similar to those in Group 2.

Group 4. Men from an infantry unit.

In all groups men were chosen who were healthy in every respect and whose previous record of health was good.

The total counts and percentages are given in Table II (p. 10). The average total leucocyte count for thirty-three men examined fasting was 8,595, and the average percentage figures for the different types of leucocyte amongst twenty-six men were:

Poly-morph.	S. Lymph.	L. Lymph.	L. Hyaline.	Eosinophil.	Mast Cells.	Transitional.
44.8	41.4	4.7	3.7	4	0.7	0.4

The total lymphocytes were slightly in excess of the polymorphonuclear leucocytes; a very distinct divergence from the normal as usually understood.

The group of patients taken as men likely to show some degree of polymorphonuclear leucocytosis were cases of nephritis; ten were examined. For these cases the average total count fasting was 11,640; whereas after a light meal it was 10,750. The average percentages of the different types of leucocytes were:

Poly-morph.	S. Lymph.	L. Lymph.	L. Hyaline.	Eosinophil.	Mast Cells.	Transitional.
68.87	28.15	2	3.32	1.85	0.47	0.25

Most of these cases presented signs of catarrh of the respiratory tract, and it was observed that the percentage of polymorphonuclear leucocytes was highest where there was fever with marked catarrhal symptoms, and that where nephritis was not associated with fever or catarrhal symptoms this percentage approached the average figure for normal men cited above.

The general summary of these observations is, that under the conditions prevailing in the north of France during this war, the average percentage of polymorphonuclear leucocytes has been found to be unexpectedly low. This observation, if confirmed by other workers, has considerable interest. The condition might be due to some general modification of metabolism, or possibly to an unusual bacterial flora in the alimentary tract. In any case it may go some way towards explaining the excessive prevalence of boils and septic sores amongst the men; for a haemopoietic system which is unable to furnish a normal number of polymorphonuclear leucocytes to the blood will probably make a deficient response to the special stimulus afforded by staphylococcal or other bacterial toxin.

The observation has also some support from the fact that papers have been published recently in which a relative or absolute lymphocytosis is described as characteristic of two different pathological conditions met with amongst soldiers evacuated to Britain.

Miller (15) (1917) considers that it is a characteristic of convalescence from poisoning by lethal gas. The normal, however, with which he compares his observations, as we understand his paper, is one quoted from Gulland and Goodall's book on the blood, not one obtained from the examination of soldiers evacuated from France who had not been exposed to asphyxiating gases.

Briscoe (16) (1917) refers to a relative lymphocytosis as one of the features of 'irritable heart' in soldiers. Here, again, the control is rather unsatisfactory in its bearing on the normal for soldiers who have recently served in France, since eight of her controls were women or medical men, and it is not clearly stated whether the remaining four who were soldiers had been abroad or not. In any case four individuals is a small number from which to obtain a reliable average. On the other hand, Dr. Briscoe's observation that in a fasting individual between 6 and 8 a.m. the lymphocytes are increased relatively by 10 per cent. would partly explain the high figures for lymphocytes obtained in our observations, since, for the sake of uniformity, all differential counts were made at that time and on fasting men with one exception. The three men in Group 4 who formed the exception were examined at noon; they, however, were found to have a higher relative proportion of lymphocytes than that found to be the average for the other groups.

Of course, in so far as Dr. Briscoe's observations refer to soldiers who have been invalidated on account of 'irritable heart' while in training at home, there is no ground for criticism of them from the above observations.

#### *Observations on Cases of 'Trench Fever'.*

Total and differential leucocyte counts were made in twenty-seven cases of the disease. The majority of these were examined during a febrile period; but some only in the intervals between febrile periods or soon after the last bout of fever. A few were examined both during and after pyrexial periods and some in successive attacks of fever.

Twenty-four counts were made on patients during pyrexia, and the average total count was 10,766. Eleven counts were made in apyrexia, giving an average total of 10,283 leucocytes. The figures for the average differential counts were:

	Poly-morph.	S. Lymph.	L. Lymph.	L. Hyaline.	Eosino-phil.	Mast Cells.	Transi-tional.
Pyrexia	65.14	21.96	4.32	4.76	2.3	0.43	0.68
Apyrexia	54.37	35	3.15	4.44	2	0.56	0.47

It is seen that there is very little decrease in the average leucocytosis between the periods of pyrexia and apyrexia, but that the figure is about

2,000 higher than that for the thirty-three normals. The absence of any marked fall in the leucocytosis in the afebrile stage is in accord with the observations of Hunt and Rankin (1) and Chambers (7).

The drop in the proportion of polymorphs is quite distinct in the apyretic period, and the difference in this respect is more marked if the three cases which were observed in both stages are considered alone. The average total counts for these were: in pyrexia 10,125, in apyrexia 12,700, and the differential counts were:

	Poly- morph.	S. Lymph.	L. Lymph.	L. Hyaline.	Eosino- phil.	Mast Cells.	Transi- tional.
Pyrexia	66.6	24.1	4.2	3	1	0.4	0.5
Apyrexia	53.5	37.6	2.7	4.9	1.8	0.58	0.66

*Technique.* In order to standardize conditions as far as possible all differential counts were made on fasting men and, with the exception of the normal men in Groups 1, 2, and 4, every one examined had been purged with castor oil, the observation being made twelve to eighteen hours after this drug had acted. The last measure was adopted because it seemed probable that varying degrees of intestinal stasis and consequent intoxication might modify the proportions of leucocytes present in the blood. As a matter of fact the average percentage of polymorphonuclear leucocytes was 6 per cent. higher in the purged men.

All counts were of 400 leucocytes. The blood films were made on slides, the spreading being done with the end of a slide which had been coated with paraffin wax, as this appeared to give a more even distribution of the leucocytes than spreading with glass. To avoid any error which might have arisen from uneven distribution of the different types of cell the count was made by passing completely across the film at either end and at various intermediate points. The stain used was Leishman's.

#### *Conclusions.*

1. That a palpable enlargement of the spleen has been a feature of at least 10-15 per cent. of the cases of 'trench fever' which have come under our observation.
2. That the average soldier in France has probably a low percentage of polymorphonuclear leucocytes in his circulating blood.
3. That 'trench fever' is associated with a moderate leucocytosis and that during the pyrexial periods the polymorphonuclear leucocytes are relatively increased.

We wish to express our indebtedness to Surgeon-General M. Irwin and to Col. Sir Wm. Leishman for affording us facilities in carrying out this investigation; to Lt.-Colonels Lawson, Thomson, Winslow, Winter, and Wraith, R.A.M.C., and to Major Gossage, R.F.C., for affording us access to patients or personnel under their charge; and to Sgt. R. E. B. Brown, B.A., and Ptes. H. Bartlett, C. Bull, and J. W. Humphries for ready assistance with the work.

TABLE I.

Authority.	Total Number of Leucocytes.	Polymorph.	Lymphocytes.	Large Hyaline.
Hutchinson and Rainy (British)	6,000	60-65 %	25-35 %	3-5 %
Naegeli (German)	about 7,000	65 %	20-25 %	5-8 % [figure for large hyalines included under transitional forms]
Stewart	10,000 [fasting may be 7,000]	65-75 %	21-26 %	3-5 %
Sahli (Swiss)	7,680 [fasting adult]	70-72 %	22-25 %	1 %

TABLE II.

Group.	Number of Men examined.	Average Total Leucocyte Count.	% Poly-morph.	% Sm. Lymph.	% L. Lymph.	% L. Hyaline.	% Eosino-phil.	% Mast Cells.	% Transi-tional.
I	12	7,741	9,975						
I	3		58.66	32.5	1.58	4.41	2	0.66	0.08
II	10	8,440	37.55	44.12	7.5	4.2	4.97	0.9	0.75
III	11	9,668	9,690						
III	10		48.8	40.06	3.29	3.28	3.73	0.54	0.24
IV			42.08	45.91	3.75	2.75	4.16	0.66	0.66

# ON THE SPLEEN AND LEUCOCYTES IN 'TRENCH FEVER' 11

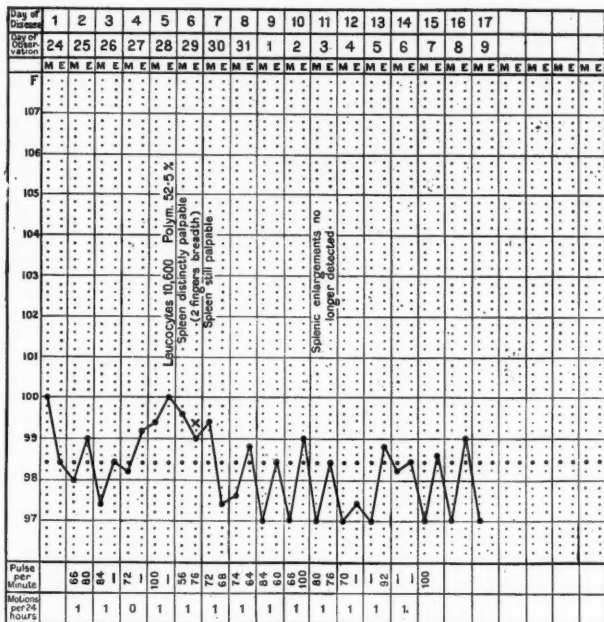


CHART 1.

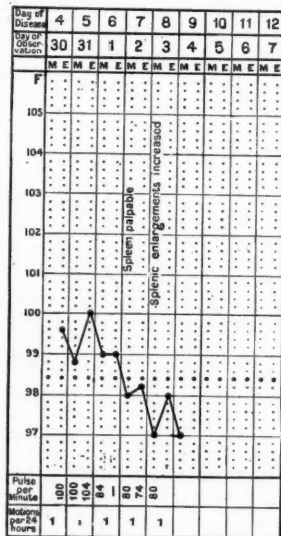
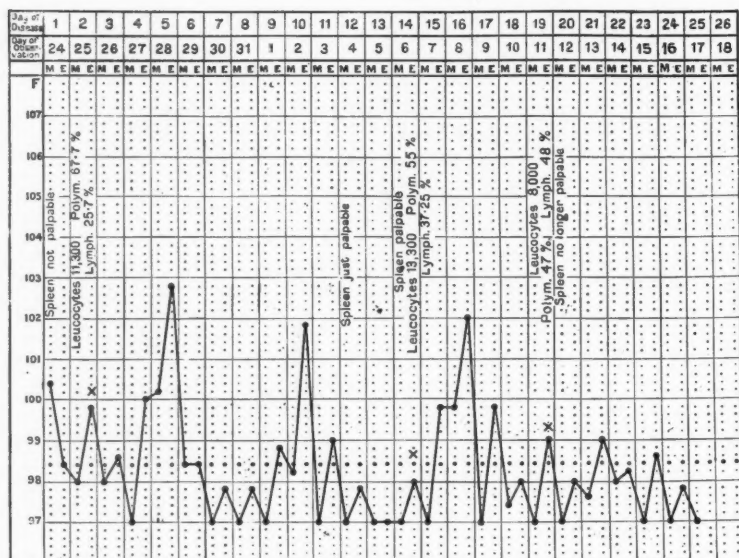
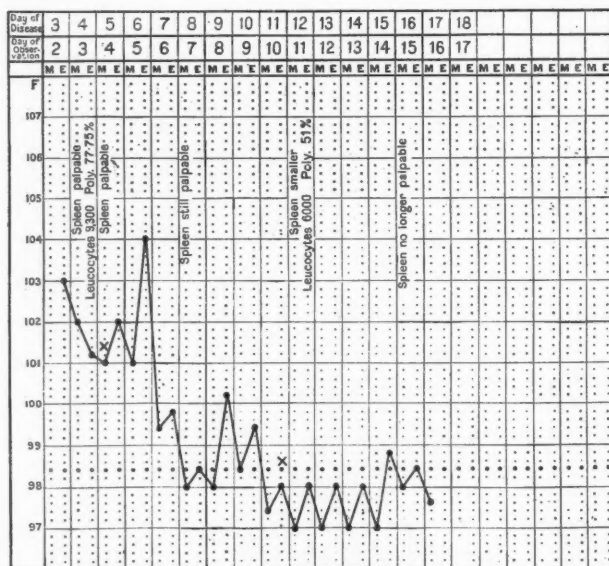


CHART 2.



X marks the points at which blood counts were made.

CHART 3.



X marks the points at which blood counts were made.

CHART 4.

REFERENCES.

1. Hunt and Rankin, *Lancet*, Lond., 1915, ii. 1133.
2. McNee, Renshaw, and Brunt, *Journ. Roy. Army Med. Corps*, Lond., 1916, xxvi. 490.
3. Hurst, *ibid.*, 1917, xxviii. 207.
4. Herringham, *Quart. Journ. Med.*, Oxford, 1915-16, ix. 429.
5. Balfour, *Official Memorandum*.
6. Coombs, C. F., *Lancet*, Lond., 1917, i. 183.
7. Chambers, *ibid.*, 752.
8. Houston and McCloy, *ibid.*, 1916, ii. 632.
9. Davies and Weldon, *ibid.*, 1917, i. 183.
10. Hutchison and Rainy, *Clinical Methods*, 5th edit., Lond., 1912, 220 and 235.
11. Naegeli (article on the Pathology of the Blood), Aschoff's *Pathologische Anatomie*, 3. Aufl., Jena, 1913, 160-161.
12. Stewart, G. N., *Manual of Physiology*, 7th edit., Lond., 1914, 19.
13. Sahli, *Diagnostic Methods*, 2nd edit., Philadelph., 1914, 764.
14. Walker, Hall, and Adam, *Lancet*, Lond., 1916, ii. 514.
15. Miller, *ibid.*, 1917, i. 793.
16. Briscoe, *ibid.*, 832.



# ON THE PATHOGENESIS OF DIPHTHERITIC PARALYSIS

By F. M. R. WALSHE

## PART II

### CLINICAL OBSERVATIONS ON THE PARALYSIS OF FAUCIAL AND EXTRA-FAUCIAL DIPHTHERIA, WITH AN ANALYSIS OF THIRTY CASES FOLLOWING SKIN AND WOUND INFECTIONS

#### I. INTRODUCTION.

THE present paper is based upon the examination of a large number of cases of post-diphtheritic paralysis, following faucial, cutaneous, and wound diphtheria. In the outbreak with which these cases were associated there occurred, side by side with the well-known clinical picture of diphtheritic paralysis with its palatal, ocular, and generalized symptoms, a distinct and equally characteristic symptom-complex following secondary diphtheritic infections of wounds and cutaneous lesions ('septic sores').

The opportunity of studying a large number of cases of nervous sequelae after extra-faucial diphtheria is one that occurs but seldom, and an analysis of thirty cases of this type is included in this paper. For purposes of comparison, however, a general description of the nervous syndrome as it appeared after the faucial infections is given, and serves to emphasize the distinctive character of the paralysis of extra-faucial diphtheria and throws an important light on the pathogenesis of diphtheritic paralysis in general. For, as I have pointed out elsewhere (17), the paths by which the toxins of diphtheria reach the nervous system have never been clearly elucidated, and the cranial nerve involvement, so characteristic of the nervous sequelae of diphtheria, has not yet received an adequate explanation.

Most clinical and experimental observers have regarded the nervous complications of diphtheria as the result of a selective haematogenous toxæmia of the nervous system. Thus, in 1900, Remak (14) on this point speaks of the 'zur Zeit herrschenden Lehre, dass ein vom Diphtheriebacillus erzeugtes im Blut kreisendes Gift die späteren Nervenstörungen verursacht'. And again, 'Der spezifischen Localisation und Entwicklung der postdiphtheritischen Nerven-symptome dürfte aber auch eine entsprechende Localisation der neuritischen Prozesse entsprechen. Für diese hat man keine andere Erklärung, als dass eine



besondere Affinität oder Prädilection des Diphtheriegiftes für bestimmte Stellen des peripherischen und centralen Nervensystems obwaltet.' More recent experimental investigations (Bolton and Bown (4), Crocq (7)) have been held to establish this view. However, certain writers have not been satisfied with this hypothesis. Mendel (14) attributed the palatal paralysis to the fact that the nerves of this structure were bathed in the toxin from the neighbouring infective focus, but Remak does not accept this on the ground that the other cranial nerve palsies are not explicable on this basis. Babonneix (2) in 1904, and Guillain and Laroche in 1909 (8), put forward the view that the process was of the nature of an ascending neuritis from the infective focus, analogous to the nervous involvement in tetanus and rabies.

Nevertheless, these views have not obtained wide acceptance, and a selective haematogenous toxæmia is commonly invoked as the cause of diphtheritic paralysis. In a recent analysis (17) of these experimental results, and a comparison of them with the paralysis following faucial and extra-faucial (wounds and skin lesions) diphtheria, I was able to advance strong evidence of a close anatomical relationship between the site of the infective focus and the incidence of the initial paralytic symptoms; evidence going far to prove that in diphtheritic paralysis, as far as its initial symptoms are concerned, we are dealing with an ascending perineural lymphatic intoxication of the nervous system, of the type called by Orr and Rows (13) 'lymphogenous toxi-infection of the nervous system'. For, if the current theory of a selective blood-borne toxæmia be correct, the syndrome of diphtheritic paralysis should be constant in its clinical evolution and incidence, irrespective of the site of the infective focus. If, on the other hand, it is found that the paralysis shows 'local sign'—to use a phrase borrowed by Sherrington from psychology—in its development, it is clear that this view must be modified, and we must consider the possibility of a 'lymphogenous' process of the type described playing a part in the production of the paralysis.

Herein lies the interest of the present series of cases which helps to elucidate the pathogenesis of the condition. This yet remains, in spite of numerous and exhaustive experimental and histological investigations, obscure and the subject of conflicting views. It is with this point in view, rather than with the idea of giving a detailed description of a condition familiar to every clinician, and the subject of so many comprehensive studies, that the present series of cases has been recorded.

## II. CLINICAL.

### *General Account of Cases.*

During the winter 1916-17 a number of cases of typical post-diphtheritic paralysis came under observation, associated with the occurrence of diphtheria among troops in the field. Early in 1917 there appeared occasional cases of

a mild type of multiple neuritis, without preceding cranial nerve involvement, and not associated with any history of sore throat or other illness. A consideration of the circumstances under which they arose justified, it was thought, the exclusion of beri-beri, arsenic, and other common causes of this affection. They were, therefore, provisionally diagnosed as 'toxic polyneuritis of unknown origin'. One feature possessed in common by all these obscure cases was at first disregarded, namely, the recent occurrence in the patients of 'septic sores', a condition in which small superficial areas of ulceration develop on the dorsum of the hand, the extensor surface of the forearm, and round the knees. These lesions were known to the Australian troops as 'barcoo rot', and have been described by C. J. Martin (10) under this name, from the point of view of their bacteriology.

These sores were so common that their presence was not at first sight remarkable or significant. However, owing to the prevalence of diphtheria, the possibility of the secondary infection of the skin lesions by the diphtheria bacillus seemed a conceivable explanation, though the absence of cranial nerve symptoms in these cases seemed against such a view. During April 1917 the following interesting case was seen which made this suggestion appear more reasonable. A medical officer, in performing tracheotomy on a case of laryngeal diphtheria, infected the right thumb and developed a pure diphtheritic ulceration associated with severe toxic symptoms: albuminuria, vomiting, and cardiac arrhythmia. This was followed by a multiple neuritis with no ocular or palatal symptoms, and starting with a marked ataxic paresis of the right hand and arm. In August a second similar case was observed, that of a man who had received a flesh wound in the buttock in April. The wound had never healed in spite of the use of every old and recent antiseptic. During August he was allowed to walk about, and at once developed signs of multiple neuritis without ocular and palatal symptoms. Examination of the wound revealed a small unhealed area from which a pure culture of the diphtheria bacillus was obtained. A full report on these two cases has already been given by the writer in the paper alluded to earlier.

During the summer of 1917 several observers recorded the finding of 'diphtheroid rods' in septic sores in the area of operations in which diphtheria was prevalent. From this period onwards numerous cases of wounds and septic sores followed by polyneuritis were observed. Unfortunately, in the majority of instances, the primary lesion was healed before the cases came under observation for nervous symptoms, and bacteriological confirmation of the nature of these was not obtainable. However, the first case mentioned above was clearly associated with a true diphtheritic infection, the source being a fatal case of laryngeal diphtheria. In four others an organism morphologically and in its cultural reactions indistinguishable from the diphtheria bacillus was isolated from the lesions. There is little doubt that all the remaining cases observed were diphtheritic in origin also, for not only were they associated in point of time and place with the occurrence of faucial diphtheria and of post-

diphtheritic paralysis, and with the isolation by numerous observers of diphtheroid organisms from the particular type of skin lesions which all these cases showed, but they presented in several instances a clinical feature very characteristic of diphtheritic paralysis, namely, paresis of accommodation.

The absence of any other ascertainable cause for the occurrence of multiple neuritis in such frequency must also be taken into account. Taken as a whole there seems sufficient evidence for describing these cases as diphtheritic in origin, and as such they are here recorded. As might be anticipated, cases have been observed in which both faucial diphtheria and septic sores were present. In certain of these it is difficult to ascertain which was the primary source of infection, and in them examples of both types of paralysis have been observed. In other cases no evidence of either septic sores or faucial diphtheria was obtainable, nervous phenomena, such as paralysis of the palate or multiple neuritis, being the first sign of disease.

The cases are grouped as follows for purposes of description: (1) General account of the nervous phenomena following faucial diphtheria. (2) Analysis of thirty cases of multiple neuritis following cutaneous and wound infections. (3) Note on possible double infections. (4) Paralysis with undetected source of infection.

1. *The nervous symptom-complex of faucial diphtheria.* In the great majority of cases nervous symptoms appeared in the usual way by regurgitation of fluids through the nose and nasal voice. In those who were under observation from the onset of the illness a profound bilateral paralysis of the soft palate was observed to develop rapidly. In one case, in which the local lesion was more severe on the right side, the palatal palsy remained throughout much more marked on that side and was very slight on the left. Aubertin and Babonneix (1) record this association, the significance of which is, in view of the hypothesis advanced here, clear. Palatal paralysis developed as early as the sixth or as late as the thirty-fifth day, and persisted for from two to twelve weeks. In the more prolonged cases recovery was gradual, and transient reappearance of regurgitation, or of 'loss of voice', was associated with fatigue, such as was produced by talking too freely. In no instance was laryngeal or pharyngeal paresis observed, the loss of voice complained of by patients being the nasal intonation associated with palatal paralysis, and deglutition was always possible. Equally frequent was paralysis of accommodation. The onset corresponded very closely in point of time with that of the symptoms described above, but on the whole was a few days later in appearing, and only once lasted longer than two weeks. In two cases it occurred without any palate symptoms, while similarly in a few instances palatal paralysis occurred without ocular symptoms. To testing in the ordinary way a reaction to accommodation could always be obtained, and the patient appeared able to read for one or more minutes before difficulty was noticed. No other ocular paralysees were noticed.

No sensory symptoms referable to the fifth nerve were noted, but several

cases, during the stage of cranial nerve involvement described, showed marked tenderness to pressure of the masseters and temporal muscles.

Another noteworthy phenomenon was the frequent weakness and tenderness to pressure of the sterno-mastoids. It is thought that this paresis should be regarded as analogous in origin with the palatal defect. Rolleston (15) speaks of it as one of the later paralyses, but my experience suggests that it may be demonstrated earlier than the generalized paralysis if sought for.

A facial palsy, sudden in onset and lasting about twelve days, was noted in three cases associated with palatal and accommodation paralysis. No other cranial nerve defects were observed.

*Multiple neuritis* followed in almost all observed cases, usually as the symptoms just described were clearing up. It is difficult, however, to date the onset accurately, as the first symptoms were frequently very abrupt in appearance and followed very rapidly the man's discharge to detail camp. That is, the patient became aware of weakness and aching of his legs, unsteadiness of gait, clumsiness and weakness of the hands, and paraesthesiae on his return to conditions of physical activity. A single route march often sufficed either to produce or to unmask a very profound weakness of the limbs. Concurrently, palpitation, shortness of breath, giddiness, and faintness on exertion were commonly complained of.

On examination, these patients always showed, even when lying still, a degree of tachycardia ranging from 85 to 100. Sudden movements caused a rise in the pulse-rate to as much as 130. Examination of the nervous system revealed a varying degree of weakness of neck, trunk, and limb musculature, ranging from slight paresis to profound weakness. In the lower limbs the peronei and dorsiflexors were most severely hit. In the case of the upper limbs no such selective weakness was observed. In no instance was there more than a slight generalized wasting of muscles.

The distal limb muscles, small hand muscles, calves and plantar muscles, were constantly and markedly tender to pressure. In this connexion the comparatively slight degree of hypersensitiveness of the antero-external group of muscles in the leg, as compared with the frequently exquisite tenderness of the calf muscles, was noteworthy.<sup>1</sup> No definite diaphragmatic paresis was noted.

A degree of sensory ataxy was constantly present, and as constantly complained of by the patient. It could be demonstrated in the finger-nose test and as a definite Rombergism when the eyes were closed. It was sometimes very evident in all movements. Inability to handle a rifle, to shave, to write, or to do up buttons, and staggering gait when tired, were constant symptoms.

On the sensory side paraesthesiae were constantly complained of; feelings of 'pins and needles', of 'numbness', 'deadness', 'stiffness', and coldness in the

<sup>1</sup> I have often remarked this contrast in injuries of the sciatic nerve. These two groups of muscles are innervated by the external and internal popliteal nerve respectively. Perhaps the 'causalgia' peculiar to internal popliteal nerve lesions may be another aspect of the same pathological phenomenon.

hands and feet. Objectively, impairment of cutaneous sensibility to all forms was noted, most profound over the distal extremities, and reaching up the fore-arms and to the knees, where the area of change merged gradually into normal sensation. Over fingers and feet complete anaesthesia to cotton-wool was often found, but never such profound loss to pin-prick and temperature. Sense of position, appreciation of passive movement of fingers and toes, was often grossly defective, causing the sensory ataxy referred to, and was occasionally manifested as pseudo-athetosis of the hands. Vibration sensation was always impaired early and, compared to cutaneous sensibility, deeply. It was in several instances completely lost below knees and elbows. On the whole, deep sensibility was always more profoundly involved than cutaneous forms.

The study of the reflexes was of particular interest. The abdominal reflexes were always conserved, as were the plantars, except in two cases of profound paralysis in which plantar stimulation gave no response. When present they were always normal in type.

A series of six cases was observed almost continuously from the onset of the infection; the rest were men returned from convalescent dépôts or detail camps, where they had gone sick with symptoms of polyneuritis and such manifestations of toxæmia as tachycardia, palpitation, and shortness of breath. It appeared from all these that loss or diminution of knee- and ankle-jerks was not the earliest sign of multiple neuritis. Numerous cases were examined before these reflexes had disappeared, which they did in due course, and all showed well-marked objective and subjective evidences of neuritis during this period of the conservation of the tendon jerks. Moreover, in the six referred to above, a very definitely increased facility of these reflexes preceded their diminution and abolition. In every instance, too, the ankle-jerk was the earlier affected, growing feeble before the knee-jerk lost in facility, and disappearing while this was still obtainable.

Since it is frequently stated that this initial phase of tendon reflex exaltation in neuritis is exceptional and rare (Déjerine, Oppenheim), an account of two cases in which it was possible to observe the variations in these from the onset will be of interest.

*Case I.* Capt. B. Sore throat on 17.11.17. The swab was found positive and 4,000 units of antitoxin given.

On 26.11.17 regurgitation of fluids and nasal voice were present. Examination showed that the right half of the soft palate was immobile, the left half paretic. No ocular symptoms appeared then or later.

On 6.12.17 a noteworthy increase of knee- and ankle-jerks was observed for the first time, and also a definite tenderness to pressure of the vasti, calf, and plantar muscles. There were no objective or subjective sensory changes. Tachycardia and albuminuria were present.

Nasal voice and regurgitation of fluids through the nose continued for nearly three months, clearing up very gradually. While they were still just present on 1.2.18, it was noted that the ankle-jerk was becoming sluggish. The calves were still very tender, and there was an appreciable weakness of dorsiflexion over and above the general weakness.



On 11.2.18 both knee- and ankle-jerks were absent.

During February he began to complain of 'stiffness' and 'pins and needles' in the fingers and toes, and a mild degree of paresis developed.

At this time (11.2.18) also slight objective blunting of touch and slight sensory ataxy of the fingers were noted.

In this case objective signs, muscle tenderness, and weakness preceded paraesthesiae and tendon areflexia by several weeks. Also an initial stage of reflex exaltation was seen.

*Case II.* L.-Cpl. D. Sore throat on 3.8.17. The swab was negative and no antitoxin was given, but he appears to have been retained in hospital for treatment of septic sores.

Came under observation on 15.9.17 for change in his voice, which was definitely nasal in quality. There was no actual regurgitation of fluids, but he 'felt a lump at the back of the throat' when swallowing. These symptoms and a 'blurring of sight' when he tried to read had been present for a week, while for several days he had begun to notice himself 'blown' if he walked any distance, and weak and markedly unsteady on his legs, so that he staggered. In addition his feet and fingers had felt 'funny and unnatural'.

Examination revealed a brisk pupil reaction to accommodation but ready fatigue on reading. There was a nasal intonation of the voice but no regurgitation, and the palate moved fairly well on phonating. The sterno-mastoids were weak and tender to pressure.

When lying down the pulse-rate was 80.

The limbs showed no definite weakness, but the calves, palmar and plantar muscles were somewhat tender to pressure.

There was indefinite blunting of sensation over fingers and feet, mainly of position and vibration sensations. The tendon jerks were all very facile.

On 1.10.17 calves were very tender, and he complained of aching pains if he walked more than a few yards. The knee-jerks remained facile, the ankle-jerks sluggish.

On 17.10.17 both knee- and ankle-jerks were absent. After this the neuritis developed for about four weeks, so that the patient could only walk with support. The tendon jerks were still absent in November, when he was evacuated overseas.

In these the development of polyneuritis was observed, and the loss of the knee- and ankle-jerks was seen to be antedated by other objective as well as by subjective signs. Their slow disappearance in the three cases described is doubtless referable to favourable conditions of rest and treatment. In the return cases, in which they were present on coming under observation, the reflexes disappeared much more rapidly.

Another constant phenomenon was tachycardia. This varied in degree with the severity of the paralytic condition. In all the cases of diphtheritic paralysis described in this paper none showed a normal pulse-rate. Daily observations for over three weeks, on ten patients in a ward at one time and confined to bed, showed that the average pulse-rate was between 80 and 85. Three severe cases had pulses constantly over 85, often over 90. In one there was also cardiac arrhythmia, but in the rest no other objective cardiac physical signs were detected.

Thus far, I have described the full symptom-complex of post-diphtheritic paralysis, and this was present in the majority of observed cases. In a certain

number, however, palatal paralysis, alone or associated with accommodation paralysis, was the sole manifestation, while in some instances a mild grade of polyneuritis developed in from two to four months without any preceding palatal palsy. Accommodation paralysis was not observed as an isolated phenomenon.

Among the late mild cases of polyneuritis not associated with local paralyses were included those in which no very definite subjective symptoms of neuritis were present. Often the patient did not complain of paraesthesiae or loss of sensation in the extremities. Ready fatigue, breathlessness, and general weakness constituted the most definite symptoms. Examination of these patients revealed absence of tendon jerks, increased sensitiveness of muscles to pressure, and indefinite general weakness and muscular hypotonus. On the sensory side, beyond an inconstant blunting of vibration sensation no objective loss was observed. These are evidently the cases of loss of reflexes after diphtheria so commonly described. A certain vagueness surrounds the question of diminution and abolition of the tendon jerks in diphtheria. These variations, according to some writers (Rolleston and others), may be present as isolated phenomena in otherwise normal extremities.

If disappearance of these reflexes be regarded as the first sign of diphtheritic polyneuritis (Oppenheim) this is readily comprehensible. However, Rolleston (16), in a study of the tendo Achillis jerk in diphtheria, does not seem to take this view. He appears to regard tendon areflexia as not necessarily associated with polyneuritis, and conversely, although he recognizes a rough parallelism between them. This author, in a series of a hundred cases, describes abolition of the knee-jerk in sixty-nine and of the Achillis jerk in forty-seven. Of these only a certain proportion were considered to have paralysis.

In an examination of fifty convalescent uncomplicated cases of diphtheria, in the second to fourth weeks of their illness, no trace of any alteration in the knee- or ankle-jerks was noted. Further, in every case of local palatal palsy followed by polyneuritis, there were present other unequivocal signs of polyneuritis: weakness, ataxy, muscle tenderness, paraesthesiae, and objective sensory changes before these reflexes disappeared.

The evolution of the generalized symptoms of diphtheritic polyneuritis in the six cases studied from the onset was as follows: During the second week of the illness knee- and ankle-jerks were extremely facile, beyond normal limits. As the palatal and ocular symptoms were subsiding, and before any fresh objective symptoms were complained of, examination revealed an increasing and abnormal tenderness to pressure of the calf muscles, then of the small hand muscles. Later, the patients complained of paraesthesiae in fingers and toes and frequently of clumsiness of the hands. When these phenomena were well established, a progressive diminution, proceeding to loss, of knee- and ankle-jerks was noted. In every case the ankle-jerk was the first to go, as in recovery it was the last to reappear.

Nevertheless, a certain number of cases were observed of a delayed, low-grade polyneuritis in which absence of knee- and ankle-jerks was certainly the

most striking, possibly even the earliest, sign. This was not true of the cases following palatal paralysis however. In these, tendon arreflexia was neither the sole nor even the earliest objective sign, and it may be questioned whether it ever occurs in otherwise normal extremities.

It is quite possible that in patients, infants for example, who did not complain of paraesthesiae, an examination directed solely to the state of knee- and ankle-jerks might lead to the view that absence of these was an isolated phenomenon. It is, indeed, extremely probable, first that in the evolution of a polyneuritis, whatever its cause,<sup>2</sup> a transient exaltation of the tendon jerks precedes their diminution and loss. Secondly, that, in diphtheria, variations in these reflexes obey the same laws as in every other polyneuritis, and do not exist apart from this condition. Further, the present series of cases does not confirm the observation of Rolleston (16) that the knee-jerks are more commonly altered than the Achillis jerks. If this is the rule then diphtheritic polyneuritis is unique in this respect. Bramwell's (6) observations on the Achillis jerk in peripheral neuritis are also opposed to Rolleston's experience. The relatively late disappearance of the knee-jerk in incipient diphtheritic paralysis has a practical significance under present conditions, since, using its presence as a criterion, I have known medical officers regard as fit men who were undoubtedly developing a polyneuritis.

2. *Analysis of thirty cases following wounds and skin lesions. The infective focus.* In these cases the primary lesion was the wound associated with a 'boil', cut, or gunshot, or a 'septic sore'. Certain observers have thought from the bacteriological findings in septic sores that these are primarily diphtheritic in origin. The present series of cases, in which, of a total of thirty, paralysis followed infected gunshot and other wounds in eleven, suggests that we are dealing with a secondary infection of pre-existing lesions. Not only is this inherently more probable, but when we consider that they all arose in an area in which faucial diphtheria was prevalent it is not surprising that a certain proportion of these lesions should become infected. It has also been suggested that, 'septic sores' being primarily and essentially diphtheritic, skin lesions are the source of the faucial diphtheria present in the same area. There seems no evidence in support of such a view.

In all but four instances the cutaneous foci of infection were healed when the cases came under my observation. At this stage the healed septic sore presents scars of two principal types. (1) In the smaller sores it consists of a small irregularly round reddish-purple area in which the texture of the skin may be normal, or in which there may be a sharply circumscribed central area of shiny atrophic skin. In time these become paler and ultimately almost fade

<sup>2</sup> In the case of beri-beri, in which large-scale human experiments (Fraser and Stanton and others) have been carried out, and the earliest signs of the disease carefully sought for, this preliminary tendon reflex exaltation is very commonly recorded. Under equally favourable circumstances it would probably be found true of other forms of multiple neuritis.



to normal pallor. In cases uncomplicated by neuritis a sensory examination of these revealed no defect. On the other hand, in cases associated with polyneuritis, some of the sores showed definite impairment of sensory acuity to touch and pin-prick. This did not appear to depend on tissue destruction and scarring. (2) The typical larger sore consisted of a sharply circumscribed area of pale, shiny, hairless skin, pink when recently healed, over which was dotted small irregular raised naevoid patches, or of a central nodular keloid area in the wounds, cuts, &c. This area is surrounded by a zone of brownish pigmentation on skin of normal texture, with a sharp inner margin and an irregular, ill-defined, outer margin. The appearance is as though all the normal pigment of the skin involved in the original lesion had been washed up to a high-water mark round the scar.

When situated on a digit this form was necessarily less well seen owing to wrinkling of skin over flexures and narrowness of the available area. In these there was always profound, sometimes complete, sensory loss, and in most cases a zone of graded sensory change passing imperceptibly into normal sensibility externally. In some instances this zone was from one to two inches in depth, and in the case of the wound recorded already (17) was even wider.

While it is probable that the anaesthesia of the scar itself is due to tissue destruction, this explanation does not account for the sensory loss in the smaller sores, nor that of the zone of normal skin surrounding the larger lesions.

If, as will subsequently be discussed, we are dealing with an ascending perineural toxi-infection, of the class described by Orr and Rows (14) as 'lymphogenous toxi-infections of the nervous system', this sensory loss may be dependent on pathological changes in the afferent nerves by which the toxin is conveyed, and which subserve the area of skin involved.

*Symptomatology.* The clinical picture as seen in thirty cases showed a remarkable constancy. Palatal symptoms were absent in every instance. In ten, paralysis of accommodation occurred simultaneously with the multiple neuritis. In two, a transient facial palsy was noted. In eight of the total there was evidence of 'local sign' in the development of the condition, i.e. of an anatomical relationship between the site of the infective focus and the onset of the neuritis. This point is so significant that some details will be given.

Of the thirty cases recorded, twelve followed a single infective focus and eighteen were associated with multiple skin lesions. Those which showed this focal development were with two exceptions of the former class. The exceptions occurred, however, in men in whom, although there were numerous 'septic sores', yet there was in each instance one large sore which had been more severe and longer lasting, and which one may presume was the actual infective focus. In the eight cases which showed a local onset related to the infective focus, this focus was in four on a digit (finger or toe) and four times on the antero-lateral aspect of the leg just below the knee.

The scars presented the characteristics recorded above and were of the smaller variety in three and of the larger in five. In several of these cases

paraesthesiae, weakness, ataxy, and aching pains in the limb which was the site of the infective focus ushered in the development of a polyneuritis. In others, however, the patient did not record this local onset, but examination revealed a more profound motor and sensory defect in this limb. A case in which both initial onset and most severe neuritis occurred in a limb is one that I have recorded elsewhere. When this local sign did not appear the polyneuritis developed as, and was not distinguishable from, that following faucial diphtheria, and does not, therefore, need a separate description. The reflex changes already described were present also in these. In several men who had reported sick with weakness, ataxy, and paraesthesiae in hands and legs, the reflexes were still present, but disappeared under observation. When observed in men who had 'carried on' while the septic sores were present it was found that the nervous symptoms appeared very constantly in the sixth to eighth weeks after the development of these lesions.

One other feature, however, demands description, and this was the presence in ten of a history of paralysis of accommodation. This rarely preceded the generalized symptoms; it usually accompanied their evolution. I was only able to observe it in two, but it was clearly elicited in the history of the other eight, and often the patient volunteered the statement that his vision had been affected. It does not therefore seem possible to disregard this evidence. The following case is an example of this:

*Case IV.* Lt. Hip. received a gunshot wound just below the left knee on 2.11.17. The two bullet-holes—entry and exit—lay three inches apart, the track running through muscle. This track became very septic and was laid open on 6.11.17. Subsequently he developed scarlet fever and the wound became deeper, exposing the shaft of the tibia. During December a thick membrane formed constantly on the wound, and bacteriological examination revealed the presence of the diphtheria bacillus. On 23.12.17 he received 12,000 units of antitoxin and the wound made at once a notable improvement.

On 8.1.18 he began to complain of difficulty in reading, and on 14.1.18 he was observed to have a marked paresis of the right face as well as paresis of accommodation.

He came under my observation on 18.1.18. Paresis of accommodation remained, the facial palsy was clearing up, but remained very evident. There was no evidence of palatal affection.

The knee- and ankle-jerks were very brisk, but there was some increased tenderness of the calves, and movements of dorsi- and plantar-flexion were decidedly weaker on the left side than on the right. This did not seem due to any actual involvement of the nerve in the wound, which was situated on the front of the leg.

On 5.2.18 the face was normal and the paresis of accommodation was slowly passing off, but he complained of pins and needles in fingers and feet—more especially in the left foot. His fingers were clumsy in doing up buttons and writing. Examination revealed a profound paresis of the left leg with marked wasting, definitely exceeding the wasting and paresis of the upper and right lower limbs. Both calves were exceedingly tender. There was slight loss of position sense in extremities, but cutaneous sensibility was intact.

The knee- and ankle-jerks were brisk.

On 21.2.18 the knee-jerks were still facile, but the right ankle-jerk was feeble and the left unobtainable.

In this case, which also illustrates the relation of reflex variations to other physical signs in a developing polyneuritis, there is seen paralysis of accommodation and the appearance of a local paresis related to the infective focus.

3. *Paralysis following possible double infections.* With the occurrence of faucial diphtheria among troops in whom 'septic sores' and other injuries were present it would not be surprising if the cutaneous lesions also became infected secondarily in a certain proportion. Conversely, a man with a diphtheritic ulcer on his hand might well convey the infection to his tonsils. It is possible that the ten cases described above may owe the paralysis of accommodation they presented to such a secondary faucial infection. It is, however, extremely improbable that this symptom can be so explained. The constant absence of palatal symptoms in these cutaneous cases is strongly against such a view.

Nevertheless, two observed cases of paralysis following numerous and severe septic sores were very probably secondary to a faucial infection. One of these had severe toxæmic symptoms such as were not commonly observed in the septic sore infections.

*Case V.* During October and November Pte. Bas. developed numerous septic sores on hands and legs. Those on the legs were very painful and severe and lasted six weeks.

During this time he began to feel 'done up' and was sent to hospital. There was no history of sore throat.

During the third week in December he noted that his jaws felt stiff, fluids began to flow back through his nose, his voice went, and he could not see to read or focus any near object. The muscles of his neck were painful and ached, and if he sat up (as he was apparently allowed to do) he could scarcely hold his head up.

On January 4 he awoke with a right facial palsy. At this time also he found his left foot (the site of one of the largest sores) numb and cold. Very soon both feet and hands were similarly affected, the limbs grew very weak and painful to pressure. On 23.1.18 his knee-jerks were observed to be absent.

On examination on 11.2.18, I found a pale, wasted man, with a rapid dicrotic pulse of 90.

Except for a slight nasal intonation of the voice and a trace of right facial palsy the cranial nerves were normal.

All the limbs were wasted, feeble, and ataxic in such movements as could be performed. He could not turn over in bed without assistance.

There was a typical and severe multiple neuritis.

One similar case was observed following septic sores.

In these the onset with palatal paralysis was so definite that it seems exceedingly probable that in both faucial diphtheria had supervened. Is it not likely that in the presence of one or more cutaneous diphtheritic lesions a subsequent faucial infection may cause less local and constitutional disturbance, and so pass unnoticed by a patient preoccupied, like Job of old, 'with sore boils from the sole of his foot unto his crown'?

The following case illustrates the possibility of double infections:

*Case VI.* Capt. T., during the period January-July 1917, was never free from septic sores, having as many as thirty-six at one time. However, he

carried on, though 'feeling rotten', till he developed a sore throat, which gave at once a positive swab. He received 10,000 units of antitoxin. Within ten days the sores, which had resisted treatment for months, had cleared up completely.

No paralytic symptoms appeared, and after three weeks in hospital he, somewhat prematurely, rejoined his unit in the field. After a route march his calves became painful and he felt 'thoroughly done up'; next day his hands and feet were numb and weak.

Examination on readmission to hospital revealed a multiple neuritis of moderate severity.

The reaction of the sores to antitoxin treatment suggests that they were diphtheritic in character. It seems likely that the faucial infection was secondary to these.

4. *Paralysis with undetected source of infection.* The cases observed under this heading included one of palatal paralysis with nasal voice and regurgitation of fluids through the nose in a man who, though he said that he had not been feeling 'fit' for some weeks, gave no history of sore throat and had not suffered from septic sores or any other wound or injury. The other two were cases of multiple neuritis of moderate severity arising without any cranial nerve symptoms in men who had no history of sore throat or other lesion. One of these first complained of paraesthesiae and weakness after a 'severe chill' resulting from exposure to a two-days' rain storm in cold weather. All three arose in an area in which diphtheria was occurring, and in the first instance almost certainly, and in the other two probably, followed unnoticed diphtheria. Swabs from the throats of all three were negative.

### III. THE PATHOGENESIS OF DIPHTHERITIC PARALYSIS.

Perhaps the most interesting feature of the present series of cases is the light which they throw on the pathogenesis of diphtheritic paralysis. In the introduction to this paper the accepted view that the nervous symptoms of diphtheria result from a selective action of the toxin on certain structures, and that the toxin reaches these by the blood-stream, was briefly stated. Bolton (4) and Crocq (7) from their experimental researches have also maintained this hypothesis. Bolton (4) states that 'in the higher mammals the poison especially attacks the medullary centres and the cranial nerves, and in the lower mammals the spinal centres and spinal nerves'. It is clear, however, from a comparison of experimental diphtheritic paralysis with that following faucial and extra-faucial (wounds and skin lesions) diphtheria in man that the determining factor in these apparently specific differences postulated by Bolton is a very simple physical one, namely, the site of the infective focus.

From such an analysis (17) one is led to conclude that in both human and experimental diphtheria the initial paralytic phenomena bear a close anatomical relationship to the infective focus in respect of the innervation of the structures concerned. Palatal paralysis is almost constantly the initial symptom of

involvement of nervous system in faucial diphtheria. The palatal musculature is innervated by fibres arising in the hinder end of the glosso-pharyngeal-vagus-accessorius nucleus (*nucleus ambiguus*) and carried in the pharyngeal branches of the vagus. Tensor palati, which receives its innervation through the motor branch of the trigeminal nerve, is an exception. The sensory innervation of the soft palate, uvula, tonsil, and fauces is by tonsillar branches (*circulus tonsillaris*) of the glosso-pharyngeal and also, in part, by the small and external palatine branches of the maxillary division of the trigeminal, and possibly by sensory branches of the facial nerve running through the large superficial petrosal nerve. Therefore, both the site of the infective focus and the structures paralysed are largely within the innervation of the glosso-pharyngeal-vagus-accessorius nuclear system. Associated with these anatomical facts are the findings by various observers of acute degenerative changes in these structures in diphtheritic toxæmia in man. Thus, Bolton (3) found severe chromatolysis in the cells of both vagal nuclei; that is, in those segments of the nervous system corresponding to the innervation of the infective focus.

The pharyngeal and laryngeal palsies found in severe diphtheritic paralysis, and possibly also the weakness of the sterno-mastoids, constitute, together with the palatal affection, the true 'local' paralysis. For reasons to be discussed the accommodation paralysis cannot be regarded in the light of a local phenomenon.

In striking contrast to these cranial nerve phenomena is their constant absence throughout the series of thirty cases of paralysis following extra-faucial diphtheria. Brief mention has been made of this also by Remak (14) and by Oppenheim (12) in connexion with wound and cutaneous diphtheria, and in a case described by Bolton and Brewer (5) a similar absence of cranial nerve symptoms, which may be taken as characteristic of the nervous syndrome of extra-faucial infections, was recorded. Confirmation of the view enunciated as to the origin of local paralyses was afforded in eight cases (27 per cent.) of the present series by the presence of well-defined initial local paralyses similarly anatomically related to the infective focus.

The fact that such local palsies are less constant in extra-faucial than in faucial diphtheria is not surprising, for, as Orr and Rows have found, the shorter the path from infective focus to central nervous system, the more intense the central reaction. Compared with spinal nerves the cranial nerves between fauces and brain stem have a much shorter course, and thus local phenomena may be expected to be more intense and more constant.

In the case I have described (17) of post-diphtheritic nervous symptoms following an infection of the right thumb in a medical officer who was performing tracheotomy, the development of such a local paralysis was observed. Anaesthesia of the scar of the primary lesion was noticed from the time of its healing. This was subsequently observed by the patient to spread over the dorsum of the thumb to the radial side of the dorsum of the hand. Simultaneously clumsiness of finger movements appeared. He experienced a growing difficulty in handling a pen, in doing up buttons, and in shaving. Definite



weakness of grasp and 'cramps' in the thenar and forearm muscles developed, and the limb gradually became clumsy and generally weak. Three or four weeks later, and associated with increased physical activity, weakness of the legs, paraesthesiae, and all the symptoms of a multiple neuritis came on. Examination revealed the initial and relatively more severe affection of the right hand and arm, as well as a polyneuritis, with which no palatal or ocular symptoms were associated. In seven other cases of the present series a similar initial 'local' paralysis was noted. There can be no reasonable doubt that we are dealing in these instances with a true 'local' paralysis strictly analogous with the palatal palsy of faucial diphtheria.

It has been observed that the generalized polyneuritic symptoms are the same in both faucial and extra-faucial diphtheria. In the former we find paralysis of accommodation in twenty-six out of thirty cases, in the latter in ten out of thirty. Its occurrence in both forms indicates that this ocular palsy cannot be purely of 'local' origin, though it appears more frequently when, as in faucial infections, the 'local' central nervous lesion is in close proximity to the oculomotor nuclei.

In considering these nervous phenomena of diphtheria we cannot escape the striking analogy which at first sight they present to tetanus. Meyer and Ransom (11) have divided the symptoms of this into three groups:

(a) *Local tetanus*, in which in mice and guinea-pigs, and also in man after prophylactic inoculations of antitoxin, the first symptoms appear in the immediate neighbourhood of the site of the infective focus.

(b) *Specific tetanus*: in man, irrespective of the site of infection, certain muscular areas are affected early, e.g. trismus of the jaw.

(c) *General tetanus*: if the amount of toxin is considerable, to the local as well as to the specific forms may be superadded a generalized tetanus.

Local tetanus does not occur after intravenous injection of the toxin into animals. In the case of faucial diphtheria, the palatal, ocular, and generalized symptoms may be considered to represent the local, specific, and generalized forms respectively.

As in tetanus, so in diphtheria, both faucial and extra-faucial, 'local' or 'generalized' symptoms may occur alone or in association with the 'specific' phenomena. I have not so far observed the 'specific' accommodation paralysis occurring alone after diphtheritic infections. This, however, may possibly be due to the fact that in many cases men do not 'go sick' with these transient ocular symptoms, and that, when they do, it is not to the neurologist that they are sent. Indeed, it seems almost certain that this is the correct way of interpreting these paralytic phenomena and the only way by which the clinical type of paralysis seen after extra-faucial diphtheria can be correlated with that following faucial infections.

In the matter of the pathological processes underlying the symptoms of tetanus and diphtheria it is doubtful, however, whether the analogy can be pressed. For according to the observations of Marie and Morax (9), which have

been confirmed and amplified by Meyer and Ransom (11), the tetanus toxin is taken up from the primary lesion into the adjacent lymph spaces, whence it passes into the blood-stream and thence into the motor nerves at their end plates. It is along the protoplasm of the efferent fibres that it passes to gain access to the ventral cornual cells. Though it circulates in the blood-stream it is not taken up from this by the cells. This is quite a different process from that with which the researches of Homen, Marie and Guillain, Orr and Rows, and others have made us familiar in the case of other organisms and toxins than tetanus. Briefly these observers have established the existence of perineural lymph channels and of a centripetal flow of lymph along these via the dorsal root ganglia and dorsal roots to the lymph spaces of the pia arachnoid and cord.

Numerous observers have demonstrated that in the case of peripheral infective foci, using staphylococci and other organisms or their toxic products, these reach the cord or brain-stem by this path and produce pathological lesions there. The initial local paralyses following diphtheria accord in their anatomical relationships and in the underlying nervous lesions with such a pathological process, and are explicable on no other grounds.

Moreover, Orr and Rows have shown that such anatomically related central nervous changes may occur in association with peripheral infective foci without degenerative changes in the fibres of the conducting nerve-trunk. The absence or minimal degree of *vagus* degenerative change recorded in diphtheritic toxæmia in man by Martin, Dudgeon, Bolton, and Mott do not necessarily, therefore, exclude the possibility of a direct nervous conduction of the toxin from the faucial lesion to the corresponding medullary nuclei by the perineural lymphatics.

It must be emphasized that such a process is not an 'ascending neuritis' in the strict sense of the word. Any neuritis that may occur is secondary to the passage in the perineural lymphatics of a virulent organism or toxin, and Orr and Rows believe that in the extra-medullary course of the conducting nerve, the neurilemma sheath, or perhaps the peripheral situation of the lymph spaces, confers an immunity on the nerve fibres. In the root entry zone, where the neurilemma sheath is no longer met with, the degenerative changes first appear.

There remain to be explained the ocular and generalized symptoms. These together represent the characteristic nervous syndrome of diphtheria divested of local phenomena. Does the toxin in this instance reach the central and peripheral nervous systems by the blood-stream, by the cerebro-spinal lymphatic system, or in some such way as has been postulated for tetanus toxin? The last possibility may be dismissed. Diphtheria toxin has not the exclusive selective action on motor nerve-cells that tetanus toxin has. It produces changes in other structures than the nervous system; for example, the heart. It gives rise to widespread paralyses and degenerative lesions in the nervous system after intravenous injection into animals. All the facts point to its reaching the nervous system by the blood-stream.

The possibility that, having gained the central nervous system locally as above described, it travels along the lymph spaces, reaching the cord and peripheral nerves in this way, seems equally remote. The manner in which the polyneuritis develops is against such a view. It seems much more likely that the toxin reaches all parts of the nervous system simultaneously by the bloodstream.

When the toxæmia is severe, numerous cranial nerves may also show signs of profound involvement, but in the lightest cases we frequently see only the palatal ('local') and the ocular ('specific') palsies. In short, the evidence previously advanced in favour of a double mechanism in the production of the fully developed post-diphtheritic paralysis, namely, that the local phenomena are of the nature of a 'lymphogenous toxi-infection' of the nervous system, and that the ocular and generalized symptoms are hæmatogenous in origin and part of the general systemic toxæmia, is fully borne out by the present series of cases. Such an hypothesis explains the variations in the symptom-complex according to the site of the infective focus, and renders comprehensible the difference between the diphtheritic paralysis of man and of animals.

#### IV. SUMMARY.

Examination of a series of cases of diphtheritic paralysis following faucial and extra-faucial (wound and cutaneous) infections reveals the following points:

1. That palatal paralysis does not occur except after faucial diphtheria.
2. The musculature of the palate and the region of the infective focus derive their innervation from the same source, the glosso-pharyngeal-vagus-accessorius nuclear system and its peripheral fibres, and are thus closely related anatomically.
3. Similarly in extra-faucial diphtheria the paralysis often shows (27 per cent.) an onset anatomically related to the infective focus.
4. Polyneuritis follows both faucial and extra-faucial diphtheria equally, and, irrespective of the site of the infective focus, presents a remarkably constant symptom-complex.
5. Paralysis of accommodation also follows both forms of infection, though the faucial more frequently (86 per cent.) than the extra-faucial (33 per cent.). It is, therefore, not a 'local' paralysis, and its more constant association with faucial infections may be explained by the close proximity of the local central nervous lesion in this case to the oculomotor nuclei. To this extent a 'local' factor may be admitted.
6. The grouping of the symptoms of tetanus, adopted by Meyer and Ransom, into local, specific, and generalized, may be applied equally well to the nervous phenomena of diphtheria. The palatal paralysis constitutes the 'local', the ocular affection the 'specific', and the polyneuritis the 'generalized' forms of diphtheritic paralysis. In extra-faucial diphtheria, as in tetanus, the 'local' paralysis varies with the site of the infective focus.



7. As for the pathological processes underlying this symptom-complex, it seems highly probable that as regards the local paralysis we are dealing with an 'ascending lymphogenous toxi-infection' (by the perineural lymphatics) of the central nervous system from the infective focus. The essential pathological lesion here is central and not peripheral, and is situated in the nuclear complex already described.

8. The ocular and generalized symptoms are probably the result of the circulation of the toxin in the blood-stream, whence it gains access to the whole nervous system, central and peripheral. The essential nervous lesion here is probably both central and peripheral.

These conclusions, derived from clinical observations, clearly need confirmation by experimental and pathological investigations on lines suggested by the researches of Orr and Rows and the various workers on tetanus.

Those that have been made remain inconclusive, probably from a lack of close correlation with the clinical aspects of the disease, and in part from the absence of any clear conception of the pathological processes involved.

## REFERENCES.

1. Aubertin and Babonneix, 'Paralysies unilatérales du voile consécutives à des angines diphthériques unilatérales', *Rev. Neurol.*, 1903, 172.
2. Babonneix, *Nouvelles recherches sur les paralysies diphthériques*, Paris, 1904, and *Rev. Neurol.*, 1904, No. 8, 384.
3. Bolton, C., 'Pathological Changes in the Medulla Oblongata in Acute Diphtheritic Toxaemia', *Archives Neurol.*, 1903, ii. 806.
4. Bolton, C., and Bown, 'The Pathological Changes in the Central Nervous System in Experimental Diphtheria', *Brain*, Lond., 1907, xxx. 365.
5. Bolton, C., and Brewer, 'A Case of Extensive Cutaneous Diphtheria with an Examination of the Nervous System', *Lancet*, Lond., 1905, i. 1130.
6. Bramwell, E., 'Contribution to the Clinical Significance of the Tendo Achillis Jerk', *Brain*, Lond., 1901, xxiv. 554.
7. Crocq, 'Recherches expérimentales sur les altérations du système nerveux dans les paralysies diphthériques', *Archives de Méd. Expériment. et d'Anat. Path.*, Paris, 1895, vii. 507.
8. Guillaïn and Laroche, 'From a Paper on the Pathological Physiology of Diphtheritic Paralysis', *Brit. Med. Journ.* (epitome), 1909, ii. 1379.
9. Marie and Morax, 'Recherches sur l'absorption de la toxine tétanique', (1) *Annales de l'Institut Pasteur*, Paris, 1902, xvi, No. 11, 818; (2) *ibid.*, 1903, xvii, No. 5, 335.
10. Martin, C. J., 'Observations on the Pathology of Barcoo Rot (? Veld Sore)', *Brit. Med. Journ.*, 1917, i. 761.
11. Meyer and Ransom, 'Untersuchungen über den Tetanus', *Archiv für Exper. Path. u. Pharmacol.*, 1903, xlix, Heft 6, 526.
12. Oppenheim, *Textbook of Nervous Diseases* (Bruce's transl.), Edin., 1911, i. 526.
13. Orr and Rows, 'Lymphogenous Infections of the Central Nervous System', *Brain*, Lond., 1914, xxxvi, Pts. 3 and 4, 271.
14. Remak, 'Neuritis and Polyneuritis', *Nothnagel's Spez. Path. u. Therapie*, xi. 3. 480.
15. Rolleston, J. D., 'Clinical Observations on Diphtheritic Paralysis', *Practitioner*, Lond., 1904, ii. 597 and 794.
16. Rolleston, J. D., 'A Note on the Condition of the Tendo Achillis Jerk in Diphtheria', *Brain*, Lond., 1905, xxviii. 68.
17. Walshe, 'On the Pathogenesis of Diphtheritic Paralysis', *Quart. Journ. Med.*, Oxford, 1918, xi, No. 43, 191.

## PART III

## THE CENTRAL NERVOUS LESION UNDERLYING THE LOCAL PARALYSES, A CLINICAL OBSERVATION

In the two previous parts of this paper (3) attention has been drawn to the clinical characters of the nervous symptoms after extra-faucial diphtheria (cutaneous infections). Investigation of a large number of such cases has shown that in them the palatal paralysis, so characteristic an initial symptom of the paralysis of faucial diphtheria, does not occur, but that the fully developed syndrome consists of three essential elements:

- (1) an initial local paralysis, or paresis, related to the site of the infective focus;
- (2) a specific element consisting of a paralysis of accommodation; and
- (3) a generalized element consisting of a polyneuritis.

The first element evidently replaces and corresponds to the palatal paralysis of faucial diphtheria, while the second and third are indistinguishable from these phenomena as they occur in the faucial cases.

The following conclusions were formulated as to the pathogenesis of diphtheritic paralysis: that the initial local symptoms are the result of a localized poisoning of the central nervous system, the toxin being carried along the perineural lymphatics from the infective focus to the corresponding cranial or spinal nerve-centres. In the case of the faucial infections the palatal musculature, being innervated from the cranial nerve-centre thus affected, is at once involved. The specific and generalized elements are probably due to the action of the toxin circulating in the blood-stream and reaching both central and peripheral nervous systems simultaneously.

Accommodation paralysis may therefore be regarded as the manifestation of a selective affinity of the toxin for certain elements of the nervous system, while the polyneuritis is the expression of the general toxæmia of that system. The analogy thus presented with tetanus was discussed.

According to this hypothesis the initial local paralyses are dependent on a central and not on a peripheral nervous lesion. It was pointed out in this connexion that numerous pathological investigations have indicated the vagal nuclei rather than the vagus nerves as the seat of pathological changes in acute diphtheritic toxæmia. Further, from the observations of Orr and Rows, we may conclude that negative findings in these nerves are not inconsistent with the neural lymphogenous origin of the nuclear lesions, for central nervous changes secondary to peripheral septic foci may occur without degenerative changes in the fibres of the conducting nerves.

It is clear, however, that valuable evidence on this question might be derived from a clinical study of the local paralyses themselves, if it could be determined whether they corresponded in type to a central or to a peripheral nervous lesion.

In the case of the palatal paralysis, which commonly constitutes the 'local sign' in faucial diphtheria, it is not easy on purely clinical grounds to decide this point, for this isolated involvement of a small group of muscles is not characteristic of either nuclear or peripheral lesions of the vago-spinal complex, but, in view of the relatively simple spinal segmental mechanisms, the local palsies of extra-faucial diphtheria might afford clearer indications.

Unfortunately, in many of the observed cases the infective foci were multiple and the local element was absent from the nervous symptoms. In the rest the primary lesion was situated on a digit, or on the distal segments of a limb.

In these the polyneuritis involving the same motor and sensory structures masked the characteristics of the local paresis and so prevented any determination of its central or peripheral origin. It must be remembered in this connexion that in the extra-faucial cases these local phenomena are seldom as profound, or as striking, as those of faucial diphtheria; hence the differentiation between segmental and peripheral symptoms has, in my experience, been impossible when they are overlaid by a multiple neuritis.

A necessary condition, then, is that the local symptoms shall not be followed by a polyneuritis, or that they shall be so situated that they are not involved in it. Now polyneuritis has been a constant feature of all the cases observed, while septic foci so placed as to be free from the second objection are extremely rare.

An infective focus within the territory innervated by the lower sacral cord would best fulfil these conditions, for a lesion of the cord in this region would present characteristic sphincter and sensory symptoms readily distinguishable from those of an ascending peripheral neuritic process.

Diphtheritic infections of the female genitalia, to judge from text-books of gynaecology, are not infrequent, but I have not been able to find any record of nervous sequelae of such infections. Courtney (1) has described a 'case of pseudo-tabes following diphtheritic infection of the penis', which appears to have been one of polyneuritis and accommodation paralysis, with an initial local paresis of the right arm associated with a second infected ulcer on the right hand. The state of the sphincters is, however, not recorded, while there is said to have been no sensory loss. To the general theory advanced in these papers this case may be said to add confirmation, but on the point now in question it throws no light.

It is to be expected, indeed, that cases fulfilling the requirements mentioned above should be exceedingly uncommon, but one has recently come under my observation, during the course of the outbreak of faucial and extra-faucial diphtheria I have already recorded, which appears to establish the central origin of the local lesion of the nervous system. In this instance the skin

lesion, an ulcer in the perinaeum, was healed when the patient came to notice for nervous symptoms, and hence its diphtheritic origin cannot be positively proved; but, for reasons which I have given in connexion with the earlier cases of the series, it may be regarded as such.

*Multiple septic sores on thighs and buttocks with a large ulcer in the perinaeum of ten weeks' duration. Onset of sphincter and local sensory disturbances in the seventh week. Subsequent severe polyneuritis with paresis of accommodation. Complete absence of palatal symptoms.*

Dvr. C., R.F.A., had enjoyed uniformly good health during the two and a half years of his service with the B.E.F., till the onset of the present illness. During the period November 1917 to February 1918 he had not been free from septic sores on thighs and buttocks, and at the end of this period he was admitted for a short time to hospital for treatment. After discharge, and on March 24, he noticed a fresh sore developing in the fold between his buttocks.

This was exceedingly painful and made him feel thoroughly ill. He was readmitted to a general hospital, where the sore was described as 'a deep ulcer one inch in diameter with a sloughing base and an area of red inflamed skin around. The rectum is not involved.'

During May this slowly spread and did not finally scab over till June 20, when he was discharged to a convalescent camp. During May and June, however, he had noticed that his buttocks and the skin round the anus were becoming 'dead and numb'. He lost sense of contact here when on the latrine, and found that when he rubbed his seat with his hands there was 'a dead pins and needles sensation'. To a much less degree there was a similar hypo-aesthetic and paraesthetic condition of the penis, scrotum, and the backs of the thighs.

This rapidly increased, and during June there appeared a hesitancy in passing urine, with dribbling after completion of the act. There was no impairment of the anal sphincter, but he was perplexed to find that when his motion was on the point of passing 'it seemed to go back and disappear', and it was only by inspection of the latrine that he could convince himself that he had actually evacuated his bowels.

He began to move about more freely in the convalescent camp, but soon found that the weakness that had been present after his confinement to bed in hospital increased instead of passing off. He rapidly became unsteady, 'pins and needles' appeared in hands and feet, his legs ached, and cramps came on in his calves. By July 3 he could no longer stand and was again admitted to hospital. There was no fever, and beyond a feeling of exhaustion no general symptom. There had been no palatal symptoms, and no history of sore throat.

On examination on July 6, his condition was recorded as follows:

A thin, pale man in fair general condition. Thoracic and abdominal viscera healthy. Temperature normal. Pulse-rate varies between 80 and 90 constantly. There is no oedema. Urine is normal.

**Skin lesions :** There are numerous healed 'septic sores' on both thighs and buttocks. They are round or oval in form and range from half to two inches in diameter. They present the characters already described in connexion with these lesions. Astride the fold separating the buttocks and including the anal orifice is a large irregularly outlined area of pink, shiny, atrophic, and hairless skin, two by four inches in extent, its long axis being sagittal.

In the centre of this and immediately posterior to the anal orifice is a thickened ridge of scar-tissue of one inch in length lying in the furrow between the buttocks, the focus of the original ulcer. Surrounding the whole is a zone of brown pigmented skin such as I have described. The scar is completely anaesthetic to all forms of cutaneous sensibility.

*Nervous system.* Cerebration and the special sense organs are normal. The pupils are of moderate size and react briskly to light and accommodation, but there is a ready fatigue of accommodation on reading; after a few seconds he complains that the writing 'goes all blurred'. There are no other defects of cranial nerves.

There is marked weakness of all trunk- and limb-muscles, though diaphragm and chest movements are good. The limb movements are feeble, restricted in range, and very ataxic. The latter defect is sensory in type; he cannot handle small objects; when his eyes are closed there is marked falling away of the extended hands, pseudo-athetotic movements of the fingers, and gross error of projection in the finger-nose test.

The limb-muscles are very tender to pressure, and the calves are the seat of painful cramps.

There is well-marked impairment of all forms of cutaneous sensibility over the distal halves of the limbs, increasing from a just perceptible hypoaesthesia at elbows and knees to complete loss below wrists and the lower third of the legs. All forms seem equally involved in extent and degree. Using pressure no threshold could be obtained to compasses on the palm. The sense of position and appreciation of passive movement are profoundly affected in the terminal segments of the limbs. Passive toe movements are not perceived, and there is a range of 45° of movement at the fingers before sensation is aroused. The ataxy of active movements has been described. Over the carpus and distally and below the pelvis there is complete loss of vibration sensation using a large fork (C 128). There are no trophic or vasomotor phenomena.

All tendon-jerks are abolished in the limbs. The abdominal and cremasteric reflexes are normal. There is feeble plantar response of the normal type.

The signs within the territory of the sacral segments are described separately :

*Sphincters.* The hesitancy of micturition has passed off, but there is still a slight degree of dribbling of urine. This is confirmed by the state of his linen and the faint urinous odour of the patient. The rectal sphincter is normal, and the subjective phenomena recorded have passed off.

*Sensory.* Extending over the buttocks, sacrum, penis, and scrotum, and in



a clearly-defined strip down the posterior aspect of the thighs in their upper half is an area of marked impairment to all forms of cutaneous sensibility.

This is most profound in a zone concentric with the scar (cf. Fig. 1) and including the anal orifice and the root of the scrotum on its posterior aspect. Over this region pinprick is felt as a 'tap', cotton-wool touch is not felt, hot water is felt as 'warm', and iced water conveys no temperature sensation.

Over the zone peripheral to this there is marked hypoaesthesia to these modes of sensation, and also over the strips on the thighs and on the posterior surface of the scrotum and the root of the penis. Over the anterior surfaces of penis and scrotum the change is minimal. The sacrum and coccyx are insensitive to the vibration of a tuning-fork.

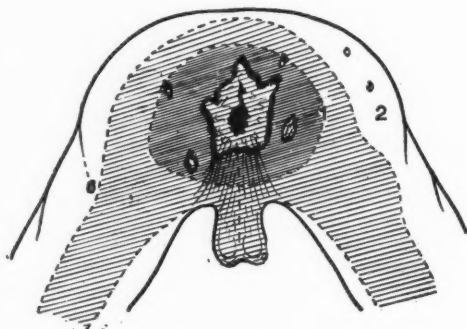


FIG. 1. (1) The perineal scar, including the anus within its periphery; and (2) the outline of the maximum area of sensory change corresponding to the cutaneous innervation of 2nd, 3rd, 4th, and 5th sacral and the coccygeal roots.

This area of sensory change is outlined in the diagram (Fig. 1), which also indicates the situation and form of the scar in the perinaeum.

The bulbo-cavernosus reflex is absent. The anal reflex is present.

Re-examination three weeks later reveals beginning regression in the sacral segmental anaesthesia. During the two weeks following his coming under observation the polyneuritis increased, but it is now arrested. The paresis of accommodation has cleared up.

This case presents the three elements of the complete syndrome of post-diphtheritic paralysis. It is in the first of these that its chief interest lies. As has been stated, the region of the nervous system within the territory of which the infective focus lay is not usually involved in a multiple neuritis. Hence any lesion arising therein can be observed in its clinical manifestations free from this complicating factor, and we have to consider whether in this instance we are dealing with an ascending peripheral neuritis, or with a central lesion produced in the manner described earlier.

The segmental distribution of the sensory loss and its extent, the sphincter defects, minimal though they be, and the absence of the bulbo-cavernosus reflex, all indicate the presence of a lesion in the sacral cord, in its second, third,



fourth, and fifth segments. No ascending neuritis in the cutaneous afferent nerves from the area of the ulcer could produce this clinical picture, and it may be concluded, therefore, that the local lesion in this instance is central, and is maximal in the segments of the cord corresponding to the innervation of the infective focus.

This is in strict accordance with the views which have been summarized earlier in this paper, and emphasizes the importance both of differentiating the local from the general pathological changes in the nervous system, when attempting to determine the essential nervous lesion of diphtheritic toxæmia by histological methods, and the necessity of correlating these methods with clinical observation most carefully.

According to Oppenheim (2) neuritis constitutes the essential basis of diphtheritic paralysis, but, in view of the changes described by numerous investigators in the central nervous system, he is constrained to add to this 'that the diphtheritic poison acts upon the whole nervous system, producing the most marked changes now at this site, now at that, but most often in the peripheral nerves, and that it may also have a toxic effect upon certain areas without producing structural changes in them'. Further, apropos of Bolton's findings in the vagal nuclei in acute diphtheritic toxæmia, he adds that 'degenerative changes found in the nerve-cells of the central organs after acute fatal poisonings cannot be regarded as the basis of the typical paralytic conditions'.

This 'definition', with the subsequent reservation, is so comprehensive and *indefinite* that any combination of acute pathological changes in the nervous system, whatever their incidence, could be included within its terms.

The clinical observations recorded in these papers do not indicate this haphazard incidence of the toxæmia on the nervous system, but reveal three definite elements in the symptom-complex, and hence three situations in which we may regard it as effected.

These are: (1) The local lesion in the segments of the central nervous system from which the infective focus receives its innervation; (2) the specific lesion in certain elements of the third nerve nuclei; and (3) the general lesion with a special incidence on the peripheral nerves. A neuritis is the basis of this, and it is comparable with the nervous lesion produced by alcohol poisoning.

#### REFERENCES.

1. Courtney, *Journal of Mental and Nervous Diseases*, 1898, 500 (abstract).
2. Oppenheim, *Text-book of Nervous Diseases* (Bruce's translation), Edin., 1911, 531.
3. Walshe, *Quarterly Journal of Medicine*, Oxford, 1918, xi. 191.

## THE RESPIRATION AND OXYHAEMOGLOBIN DISSOCIATION CURVES AND BUFFER VALUE OF THE BLOOD IN NORMAL MEN<sup>1</sup>

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THE object of this paper is to consider what experimental methods are suitable for investigating the respiration in pathological conditions, and to bring forward certain measurements on normal men to serve as a standard with which to compare similar measurements in pathological conditions.

In medicine the term 'dyspnoea' is used loosely, to include all conditions where breathing is sufficiently increased to produce discomfort. This may be due to actual obstruction in the air-passages, or may be merely due to an increase in pulmonary ventilation. It requires a very considerable increase in pulmonary ventilation to produce obvious dyspnoea. Where the ventilation is only moderately increased, the subject may be unaware of the fact, if lying at rest in bed, and it will also probably escape the notice of the observer. Every condition of increased pulmonary ventilation is commonly called 'hyperpnoea', and it is only the more severe stage of hyperpnoea to which the term dyspnoea can be applied.

The measurement of hyperpnoea is complicated by the fact that in different conditions the number of respirations per minute varies, and also the depth of each respiration, the so-called 'tidal air'. Hence it is difficult to compare quick shallow and slow deep respiration. At first sight it might seem sufficient to measure the total quantity of air breathed per minute, the so-called 'pulmonary ventilation', and to compare these figures; but here again there is a difficulty owing to the existence of a dead space in breathing, made up of the nose, throat, larynx, bronchi, &c., in which no interchange of gases takes place. It is obvious that in rapid shallow breathing the dead space will be washed out more often than in slow and deep breathing, and that therefore a greater pulmonary ventilation will be required in the former case to produce as effective ventilation as in the latter case. From this it follows that the mere measurement of pulmonary ventilation will be of no value as a measure of effective ventilation;

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what is required is a measurement of the ventilation of all that part of the lung concerned with the interchange of gases, the so-called alveolar ventilation.

This may be obtained by the following well-known method:

Let  $P$  = pulmonary ventilation,  $A$  = alveolar ventilation, then if  $D$  = dead space, the dead space ventilation will be  $RD$ , when  $R$  = number of respirations per minute.

The formula is obtained from two considerations:

(1) The volume of air leaving the lips per minute (pulmonary ventilation) will be the sum of that which has come from the alveoli (alveolar ventilation) and that from the dead space.

We have  $P = A + RD$  . . . . . (1)

(2) The amount of  $\text{CO}_2$  in the expired air will be the sum of that which has come from the alveoli and that from the dead space. Let percentage of  $\text{CO}_2$  in expired air =  $e$ , and percentage of  $\text{CO}_2$  in alveolar air =  $a$ . The percentage in the dead space, which will be the same as the percentage in the atmospheric air, may be taken as 0.03 per cent.

We have  $Pe = Aa + 0.03 RD$  . . . . . (2)

From (1) and (2),  $A = P \frac{(e-0.03)}{a-0.03}$ .

Now under ordinary circumstances 0.03 is very small compared to  $e$  and  $a$  (which have values of about 4 and 5 respectively), and may be neglected.

Therefore  $A = \frac{Pe}{a}$  . . . . . (3)

Now let  $C$  = vol. of  $\text{CO}_2$  expired per minute.

Then  $C = \frac{Pe}{100}$ .

Substituting in (3) we have  $A = \frac{100C}{u}$  . . . . . (4)

We may now write equation (1) afresh :

$$P = \frac{100C}{a} + RD \quad . \quad . \quad . \quad . \quad . \quad . \quad (5)$$

From equation (4) we find that the alveolar ventilation depends solely on two factors, the amount of  $\text{CO}_2$  expired per minute and the alveolar  $\text{CO}_2$  percentage.

Now the amount of  $\text{CO}_2$  expired varies with the state of the individual, nutrition, &c., but with the individual at rest in bed in the morning and twelve hours after the last meal, provided the latter has not contained excessive amounts of carbohydrate, the  $\text{CO}_2$  level has been found by many observers to reach a constant level for the individual.

The alveolar  $\text{CO}_2$  percentage under ordinary atmospheric pressure is practically proportional to the partial pressure of  $\text{CO}_2$  in the alveolar air, which is usually regarded as being constant for the individual, although there are slight diurnal and seasonal variations.

Hence, for all practical purposes, for individuals observed at rest in bed in the morning before breakfast, the alveolar ventilation is a constant quantity, and

any departure from the normal in pathological conditions must be due either to altered  $\text{CO}_2$  excretion, or to an alteration of  $\text{CO}_2$  pressure in the alveolar air.

From these remarks it will be evident that there is no single measurement that will suffice in order to compare the breathing of one individual with that of another. It is necessary to pay attention to a number of different factors. The pulmonary ventilation, which after all represents the total change in volume of the chest per unit time produced by the excursions of the diaphragm and thoracic walls, depends on four different factors, as can be seen from equation (5), viz. on the output of  $\text{CO}_2$ , the alveolar  $\text{CO}_2$  pressure, the volume of the dead space, and the number of respirations per minute. By using the alveolar ventilation we eliminate the dead space ventilation factor, and the result gives the effective ventilation which settles the  $\text{CO}_2$  output and the alveolar  $\text{CO}_2$  pressure.

The tidal air ( $\frac{P}{R}$ ), i. e. the volume of each respiration, and the tidal alveolar air ( $\frac{100C}{aR}$ ), i. e. the volume of air leaving the alveoli at each breath, may also be of importance in certain cases.

*Pulmonary ventilation and tidal air.* In the course of some observations by one of us on the respiration in various pathological conditions it was found that there were practically no complete data obtainable for normal individuals. One of the chief objects in undertaking this piece of work was to supply this want to a certain extent, and at the same time it was felt advisable to test the methods used before applying them more widely to pathological conditions.

The subjects of these observations were all male patients in surgical or ophthalmic wards of Guy's Hospital. From the point of view of their respiration they were to be regarded as normal individuals. The patients had mostly been lying in bed for some days before the observations were made, and so the observations will be strictly comparable to others in pathological conditions. The observations were always carried out at 9 a.m., twelve hours after the last meal. Throughout the observations the patients lay quietly in bed. The pulmonary ventilations were first measured in duplicate by collecting the expired air in two Douglas bags over a period of five minutes. The alveolar  $\text{CO}_2$  pressures were then determined by the method of Hasselbalch and Lindhard (1) and by the method of Haldane and Priestley (2), 'end-inspiration samples' being the only ones collected. Sometimes it was found possible to collect the H-L samples during the time that the expired air was being collected in the bags. For the experiments, masks made of Stent's dental wax were fashioned so as to fit the face. The junction between the mask and skin was made airtight with vaseline. Krogh rubber valves were employed. The dead space between the valves and the face was usually less than 40 c.c. The type of valves and mask is shown in Krogh's book (3). It was eventually found possible to fashion the mask either for a patient who breathed through his nose, when the nose alone was allowed to project into the air-way of the mask, the mouth being shut off, or for a patient who breathed through his mouth alone. In this case the nose was shut off from the air-way. By these means the dead space of the mask was reduced to a minimum. The resistance offered to the respiration by the mask and valves was negligible, and none of the patients complained of any difficulty in breathing. The collection of the air in the bags was not begun until some little time after the mask had been fitted, i. e. until the patient was quite comfortable and breathing evenly as far as could be seen. After collecting the

expired air, the volume was measured immediately by passing the contents of the two bags through an accurately standardized gas-meter, a sample being withdrawn for analysis of its  $\text{CO}_2$  and  $\text{O}_2$  content by Haldane's smaller gas-analysis apparatus. By this means the output of  $\text{CO}_2$  and intake of  $\text{O}_2$  and the respiratory quotient were calculated.

It will be noticed (see summary of results in Table VII) that in some cases the agreement between the duplicate determinations is not very close. However, in these cases the figures for the respiratory exchange will bear comparison with results of Benedict, Emmes, and Riche (4). These observers made on the same day a number of determinations of the respiratory exchange of certain laboratory workers. Their apparatus was probably more accurate than the Douglas bag method, especially as the duration of the experiments was longer, and the subjects were trained physiologists, well accustomed to the kind of work. In both these respects we were at a disadvantage. However, Benedict, Emmes, and Riche's results often show variations as great as ours (cf. J. M. C. (2) and J. R. (10) of their paper).

These divergences are chiefly due to irregularity in breathing. Subsequent experience has shown us that it may be necessary to take four or five samples before getting absolutely consistent results. The earlier samples may show irregularities, owing to the subject being unaccustomed to the mask and valves. However, the mean values of the earlier determinations are usually pretty close to the mean for the whole series, so that by taking the mean of these results we shall get values of sufficient accuracy for our purpose. In most cases our subjects had already practised with the mask on the day before, when the mask was fitted.

The mean value for the pulmonary ventilation was 6.060 litres per minute. The maximum was 7.55 and the minimum was 4.87. The mean tidal air was 410 c.c., the maximum was 524 c.c., and the minimum was 319 c.c. All these measurements are calculated at body temperature, and at the prevailing atmospheric pressure, saturated with moisture.

These values are considerably lower than those generally stated. Pembrey and Schlesinger (5) found, in a number of medical students, that the mean pulmonary ventilation was 7.105 litres per minute, and the mean tidal air was 425 c.c. uncorrected for temperature. The difference is that our subjects were examined resting in bed, with their metabolism at a minimum, whereas Pembrey and Schlesinger examined their cases in the course of their usual employment for the day.

*Alveolar ventilation.* The mean of our results was 3.94 litres per minute. The maximum value was 5.525, and the minimum value 3.062.

Douglas, Haldane, Hobson, and Campbell (6) have determined their own alveolar ventilations; but the results are not expressed in a manner comparable to our results.

*Respiratory exchange.* The mean value for the  $\text{O}_2$  intake was 232 c.c., and the  $\text{CO}_2$  output 185 c.c. Our results agree with those of other workers, and they do not need further comment.

*Respiratory quotient.* Our values varied between 0.725 and 0.883. The mean was 0.797. In Case A the extremely low value of 0.654 was obtained. Some error must have crept into the determination, although it is curious that the duplicates both gave low values.



*Alveolar CO<sub>2</sub> pressure.* The original method of directly sampling the alveolar CO<sub>2</sub> pressure was that devised by Haldane and Priestley (2). The subject sits breathing quietly, and after a normal inspiration or expiration breathes out suddenly and deeply along a tube, and at the end closes the tube with his tongue. The sample of alveolar air is thus obtained from just in front of the lips. The disadvantage of this method when applied to patients is the difficulty of teaching them to breathe out deeply without either taking a deep breath or holding their breath first of all. The proceeding can be somewhat simplified by using a Siebeck or Boothby-Peabody (7) valve.

Another method described by Plesch (8) consists in the patient breathing backwards and forwards into a rubber bag for about 30 seconds. The contents of the bag are analysed. This method is reputed to give consistent results, though they are systematically too high, and approximate to the CO<sub>2</sub> pressure in the venous blood. The method is probably useful in cases of rapid and shallow respiration in which other methods fail; but it is difficult to see the advantage of using it in other cases.

The method that we have found the most valuable is that described by Hasselbalch and Lindhard (1). The Stent's mask was used, and a piece of lead tubing of fine bore was brought through a side-tube on the valve T-piece, up to a distance of about half an inch in front of the nose or lips. The lead tubing was connected with a receiver filled with mercury. On turning a tap on the receiver mercury flows out under gravity, and a portion of air is drawn into the receiver from the fine lead tube. The patient lay in bed during the collecting of the sample. The observer carefully watched the outlet valve, and turned the tap for a moment just before the end of expiration, i.e. when he noticed the rubber flap beginning to fall, which indicated a lessened stream of outflowing air just before expiration finished. Each time the tap was turned a minute portion, about 1 c.c. of air, was drawn into the receiver from just in front of the patient's nose or lips. Eventually sufficient air was collected for analysis in the small Haldane gas-analysis apparatus. It is of course necessary in starting the collection of samples to see that the connecting tube is filled with alveolar air. This can be done by collecting fractions from a few breaths into the receiver and then raising the mercury to expel the sample, when the connecting tube will be left full of alveolar air. The great advantage of this method is that nothing is left to the patient. It is only necessary for him to lie quietly and breathe normally. The method can be used even when the patient is unconscious. Any unevenness in the breathing will be noticed by the observer, and no portion need be taken from any breath that is suspected of being more shallow than usual. Another minor advantage is that a sample contains portions from a number of expirations, and the resulting analysis gives a mean for the alveolar CO<sub>2</sub> pressures over the period required for taking the sample, i.e. for several minutes.

The problem we had to solve was whether a normal expiration was sufficiently large to wash out the subject's dead space as well as the part of the

TABLE I.

*Alveolar CO<sub>2</sub> Determinations.*

Hasselbalch-Lindhard Method:			Haldane-Priestley Method: End-inspiration samples.	
Subject.	CO <sub>2</sub> in mm.	Difference between extremes. mm.	CO <sub>2</sub> in mm.	Difference between extremes. mm.
A	40.3 [37.5] [37.2]	3.1	40.6 37.0 35.0	5.6
B	40.0 39.8 [38.2] [36.4]	3.6	38.0 37.1 32.5 26.9	11.1
C	41.2 40.8 [39.5]	1.7	35.7 32.3 32.1 32.0	3.7
D	39.0 [38.9] 38.8 37.7	1.3	40.6 39.8 39.7	0.9
E	42.0 41.9 41.6 41.4	0.6	42.5 40.5 38.7	3.8
F	45.4 44.0 43.9 [41.3]	4.1	50.6 46.1	4.5
G	40.9 39.8 [39.1] [37.9]	3.0	44.0 43.6 41.5	2.5
H	33.7 33.5 33.2 32.6	1.1	33.8 30.9 30.2 29.7	4.1
I	44.7 43.9 43.3 43.2	1.5	42.7 41.9 39.0	3.7
J	46.0 44.9 [43.4] 45.8 * 45.3 *	2.6	35.7	
K	38.9 37.5	1.4	37.1 32.4	4.7

\* In these samples the end of the collecting tube was placed just outside the expiratory valve (Lindhard's 'A' samples).

mask just in front of the nose, so that a sample of the true alveolar air was obtained. As a method of comparison we used the Haldane-Priestley method, getting the patient to breathe out deeply after a normal inspiration through a wide-bore tap which was closed immediately the large expiration had been made. In the later experiments we used a Boothby-Peabody valve. We did not attempt to get end-expiration samples. We found it convenient to attach an empty rubber anaesthetic bag to the end of the long tube, and by watching the filling of the bag it was easy to see the exact moment when the expiration was finished and it was necessary to turn the tap on the valve. With each of the ten patients three or four samples were collected by the two methods and analysed. The agreement between the various samples is shown in Table I, which contains all the observations we carried out.

We should expect to find the  $\text{CO}_2$  in the H.-P. samples rather lower than in the H.-L. samples, as in the latter case the alveolar air is collected at the end of a normal expiration, while the former are end-inspiration samples. The results of the H.-L. method are shown in the first two columns. The analysis of the various samples from the same subject show excellent agreement among themselves. Out of 41 analyses hardly one is obviously inconcordant. In any case, if the patient is breathing without effort, from the nature of the method it is impossible for a result to be too high, but results which are too low may be due to errors on the part of the observer, i. e. in turning the tap; for, if it is opened just after the closure of the expiratory valve, a sample of inspired air from the atmosphere will be drawn in. Some of the results, where this must have occurred, have been rejected in consequence. They are bracketed in the column. The agreement is close, because the necessary skill has been acquired by the operator, and no co-operation is required on the part of the subject.

The results by the H.-P. method (columns 3 and 4) do not agree so closely; but this is to be expected. The subject has to be instructed to take part in this operation himself, and even with trained individuals it sometimes happens that the  $\text{CO}_2$  in the end-inspiration sample is higher than in the end-expiration sample, obviously an impossibility. There is the further difficulty that the errors may be in both directions. Thus, if the subject takes in a deep breath first of all before breathing out deeply—a very natural thing to do—the result will be too low. If the subject holds his breath, or the breathing is too shallow—another possibility—the result will be too high.

This table is important as it helps to settle whether there is any systematic error in the H.-L. method, i. e. whether all the results are too low owing to insufficient washing out of the dead space by the tidal air. In eight of the cases the mean H.-L. values are higher than the mean H.-P. values, and there is no reason for supposing that this error was present. In cases F and G the mean H.-L. values are slightly lower, and, if the H.-P. values are correct, it would argue there was some deficiency in the washing out of the dead space.

We have in all cases used the H.-L. values in calculating the alveolar ventilation and the dead space, and anyhow, in the cases F and G, the error from incom-

plete washing out will not be very great. However, the possibility of this error should always be borne in mind in using the H.-L. method, and it will be safer to employ both methods where special accuracy is required.

A point of some interest is the comparatively small volume of tidal air necessary to wash out the dead space completely when the subject is breathing quietly. In Case C the tidal air was only 319 c.c., which was between three and four times the dead space (see Table II).

TABLE II.

*A Comparison between the Values for the Alveolar CO<sub>2</sub> as determined by the Hasselbalch-Lindhard and the Haldane-Priestley Methods.*

I. Results published by Boothby and Peabody.			
Subject.	H.-L. Method. CO <sub>2</sub> in mm.	H.-P. Method. CO <sub>2</sub> in mm.	Tidal Air. c.c.
	29.9	41.3	399
	34.5	38.9	440
		40.1	
II. Summary of our results.			
A	40.3	37.5	426
B	39.9	37.6	359
C	41.0	33.0	319
D	38.6	40.0	379
E	41.7	40.6	448
F	44.4	48.4	377
G	40.4	43.0	382
H	33.3	31.2	524
I	43.8	41.2	492
J	45.5	35.7	395
K	38.2	34.8	

There is another point which emerges from this table. It has been shown by Krogh and Lindhard (9) that, when the breathing is exceptionally deep, the mixing of the inspired air with the alveolar air is not complete, so that, when a forced expiration is made, the later portion of the alveolar air contains perceptibly more CO<sub>2</sub> than the earlier portions. Our results show, and Krogh and Lindhard have themselves admitted, that when the breathing is quiet and of normal depth, the mixing is complete and the alveolar air uniform in composition. Our H.-P. samples, which were taken at the end of an expiration of about 1.5 litres, agree quite well with the H.-L. samples taken after an expiration of 300-500 c.c.

There is a modification of the H.-L. method which has been adopted by various observers with the object of diminishing the dead space as much as possible. The fine lead tube is passed through the lips as far as possible towards the back of the pharynx. This method has the disadvantage of making the subject uncomfortable and possibly disturbing the breathing; at the same time

it compels him to breathe through the mouth, whereas most subjects normally breathe through the nose. Our results would seem to make this method unnecessary.

Boothby and Peabody (7) have published results throwing doubt on the accuracy of the H.-L. method. They obtained very low values for the alveolar  $\text{CO}_2$  (see Table II), viz. 29.9 mm. and 34.5 mm. with a tidal air of 399 and 440 c.c. respectively. The corresponding Haldane-Priestley samples gave values of 41.3 and 38.9 and 40.1 mm. They argued that a tidal air of 400 c.c. was insufficient to wash out the dead space completely. We can only say that their results are totally opposed to our own findings, based on a very considerable number of observations. The extremely consistent results of Hasselbalch also show the accuracy of the method.

TABLE III.

*Variations in the  $\text{CO}_2$  percentage of the Air issuing from the Mouth at the end of Expirations of different depth (Haldane, Amer. Journ. Physiol.).*

Depth of Expiration. c.c.	$\text{CO}_2$ percentage in Air issuing from Mouth after Expiration.
190	3.03
335	4.37
510	5.04
650	5.19
950	5.51
1,350	5.48

At first sight some results published by Haldane (10) are opposed to our results. Haldane made respirations of various depths and measured the composition of the air issuing from the mouth. His results are shown in Table III, from which it will appear that an expiration of 950 c.c. is necessary to wash out the dead space completely and give an accurate value for the alveolar  $\text{CO}_2$  pressure. We found that one-third of this volume was sufficient.

We think that Haldane's method did not give a true sample of the air actually issuing from the lips. To begin with, after he had made his expiration of a given depth he removed a sample large enough for analysis, whereas in the H.-L. method small fractions of successive expirations were used. This might help to account for the discrepancy if the depth of the expirations was only just sufficient to wash out the dead space. However, there is a still more important cause of disagreement. Yandell Henderson (11) has pointed out that when a gas is propelled through a tube, it does not push out the previous contents of the tube *en bloc*. Instead, in the early stages of the process, a thin cone of the gas proceeds along the axis of the tube, leaving the original gas at the side of the tube more or less unaltered. If the projection of the gas is suddenly stopped, an almost instantaneous mixing occurs between the gas cone and the original gas at the side of the tube. The practical importance of these considerations is that the collecting tube must be in the centre of the tube just in front of the lips or nose, so as to catch undiluted alveolar air in the centre of the cone of pro-



jection; further, the sample should be taken before the end of expiration. We took both these precautions in obtaining our results. Further, we arranged that the mouth of the collecting tube should be just in front of the lips or nose in the narrow part of the mask, instead of right up against the lips or nose in the wider part of the mask, because in the latter case we thought it might be possible to get impure samples from a mixture with any gas remaining in the recesses of the mask, where it fitted round the nose or mouth.

TABLE IV.

*Alveolar Air Samples with the Mask and Valves (H.-L. Method).  
Tidal Air about 400 c.c.*

CO <sub>2</sub> . mm.	Remarks.
39.5 37.9	Lead tube in front of lips. Samples collected before the end of expiration.
29.4 27.1	Lead tube in front of lips. Samples collected after expiration, with breath held.
37.3 34.0	Lead tube at back of tongue. Samples collected after expiration with breath held.
37.4 35.7	Lead tube at back of tongue. Samples collected before the end of expiration.

The importance of these precautions is seen in the preceding experiment (Table IV). The depth of the expirations was about 400 c.c., as tested in experiments by the Douglas bag. It will be noticed that the best results, i.e. the highest, 39.5 and 37.9 mm., were obtained before the end of expiration with the tube in front of the lips according to our usual procedure. When the samples were taken after expiration was finished, but before inspiration was begun, the absurdly low values of 29.4 and 27.1 mm. were obtained, which must have been due to mixing with diluted alveolar air at the side of the tube. When the collecting tube was passed to the back of the tongue, the readings tended to be too low, before and after the end of expiration, though whether this was due to altered breathing owing to discomfort or to mixing with diluted alveolar air in the naso-pharynx we do not know. It will be noted that Haldane took his samples after the end of expiration. Hence they contained, not pure alveolar air from the lips, but alveolar air mixed with diluted alveolar air at the sides of the tube.

When we were obtaining our results in 1915, we were impressed with the possibility of H.-L. samples giving too low values for the alveolar CO<sub>2</sub>, and that was why we took H.-P. samples for comparison. However, in a recent series of papers Pearce (12) claims that the H.-P. samples give too high values even when the subject is at rest and the breathing is quiet, because during the deep expiration, which is often somewhat prolonged, CO<sub>2</sub> is being given off all the time, and its concentration in the alveoli tends to increase more rapidly towards the end, as the volume of air remaining behind becomes smaller. It cannot be said that our results indicate that this error is of any practical importance, though

it may account for the high values obtained in cases F and G by the H.-P. method, viz. 48.4 mm. and 43 mm., when the H.-L. values were 44.4 mm. and 40.4 mm. respectively. The H.-L. end-expiration samples will not be affected at all by this error, even theoretically, and assuming the washing out of the dead space is sufficient they will be correct. However, it must be remembered that they will represent the highest values that the  $\text{CO}_2$  reaches during the normal respiratory cycle, and the mean alveolar  $\text{CO}_2$  pressure will be somewhat lower in each case. The method used by Pearce, of determining the mean value by analysing two respirations of different depths, would seem quite satisfactory in trained subjects, but is quite unsuitable with patients, as he himself admits.

Our results for the alveolar  $\text{CO}_2$  fall within the normal limits, with the exception of H, where the value 33.3 mm. is distinctly low. However, the agreement between all the determinations for this case makes it certain that this value was correct. The mean value for the series was 40.7 mm. or 5.8 per cent., and the maximum value was 45.5 mm. or 6.4 per cent., and minimum value 33.3 mm. or 4.8 per cent.

*Dead space.* Considerable discussion has recently taken place on the subject of the dead space in breathing. Every one is now agreed that the dead space increases with increasing inflation of the lungs. The obvious cause for this is that the bronchial passages dilate *pari passu* with the enlargement of the chest. Krogh and Lindhard (9), who have measured the dead space by means of inspirations of hydrogen, believe that the increase obtained in the dead space is due solely to this cause. Haldane (10) and Y. Henderson (11) used the Douglas bag method, which we used in this paper, and obtained a larger increase in the dead space than Krogh and Lindhard by their method—an increase which Haldane considered too big to be explained by mere passive distension of the bronchi. It might be explained by the fact that there was incomplete mixing in the lung itself, the  $\text{CO}_2$  being higher in the deeper recesses of the lungs. The high value for the alveolar  $\text{CO}_2$  leads to too high a value for the dead space as seen in equation 5. This is the explanation of Krogh and Lindhard. The error pointed out by Pearce may also come in, and this will tend in the same direction, i.e. to too high an alveolar  $\text{CO}_2$  and too high a dead space.

Haldane's explanation is on very similar lines to that of Krogh and Lindhard, except that he goes into greater detail in suggesting that the atria situated next to the terminal bronchioles contain alveolar air diluted with air from the bronchi, while in the air-sacs themselves the alveolar air is pure.

Whichever of these views is correct, our results for the dead space will not be affected, as there is general agreement that with individuals breathing quietly at rest the composition of the alveolar air is practically uniform throughout, and identical results are obtained by the method used by us and by the hydrogen method used by Krogh and Lindhard. Further, the results of the alveolar  $\text{CO}_2$  in this paper, taken at different depths during quiet breathing,

indicate that the composition of the alveolar air is practically uniform at rest.

The mean result for the dead space in our series of ten men was 105.4 c.c.; the maximum figure was 122.9 c.c.; and the minimum figure was 87.7 c.c.

It has already been pointed out that our alveolar  $\text{CO}_2$  results were the maximum results for the respiratory cycle, and that the mean alveolar  $\text{CO}_2$  percentage was probably rather lower; this would make the true values of the dead spaces found in our experiments a little lower, but the difference would be very small.

Lindhard (13) has published the following formula for calculating the dead space in men from the length of the trunk measured up to the hyoid bone:

$$\begin{array}{lcl} \text{Length of trunk} & . & = 68 n. \\ \text{Dead space} & . & = 140 n. \end{array}$$

This formula was based on observations on five men, and in two cases out of the five there was very poor agreement between the calculated and the observed values. In fact, from his cases alone, the value of the formula would appear to be extremely doubtful.

Unfortunately at the time of our experiments we did not test this formula, but we have since done so in the case of C, aged 19. His weight had fallen to 55 kilos from 58 kilos; but he otherwise appeared unchanged. He had been in the army for some months. The length of his trunk was 70.7 cm. The calculated dead space was 160.3, and the observed dead space was 87.8 c.c. A similar discrepancy was noticed in the case G, a man of about the same weight as C. The other cases were mostly rather heavier than C and G, and so there is no reason to suppose that the length of their trunks would have been any shorter. The conclusion is that Lindhard's formula is inapplicable to our series of cases, and the discrepancy is much too great to be accounted for by any error of technique or faulty analysis.

The remarkable feature of our results is that they are uniformly so low. Zuntz and Loewy's original figure (14) for the dead space measured after death was 140 c.c., and Haldane, Priestley, Douglas, and Lindhard have all reported values of similar magnitude. Our values were nearly all about two-thirds of those found by these authors.

A possible explanation is that all our subjects were investigated while lying in bed the first thing in the morning, with their metabolism at a low level. It is possible that under these conditions the walls of the air-passages are relaxed, so that the dead space becomes smaller. Another possible explanation is that the tidal air is not sufficient to free entirely the dead space from alveolar air during expiration, so that a thin layer of alveolar air is left along the walls of the passages, which thus diminishes the anatomical dead space.

*Oxyhaemoglobin Dissociation Curves of Blood*

Barcroft (15) has shown that the oxygen dissociation curve of the haemoglobin in fresh blood varies with the acidity of the blood. His method of measuring the oxygen dissociation curve consists in exposing recently defibrinated blood in a tonometer or saturator to a known pressure of CO<sub>2</sub> and oxygen in a water-bath at body temperature. The blood is then delivered beneath dilute ammonia into the differential blood-gas apparatus, without allowing air to obtain access to it. This apparatus gives, in the first place, a measure of the amount of oxygen required to saturate the blood fully, and secondly, the total oxygen capacity of the blood. From these data the percentage saturation of the blood of the given O<sub>2</sub> and CO<sub>2</sub> pressure can be calculated. Other values for the percentage saturation are obtained in other experiments using the same CO<sub>2</sub> pressure but different O<sub>2</sub> pressures. Hill has shown that a series of points representing the percentage saturation at different O<sub>2</sub> pressures lie on a curve of the following formula:  $\frac{Y}{100} = \frac{KK^n}{1 + KK^n}$ , where  $Y$  = percentage saturation,  $X$  = O<sub>2</sub> pressure in mm., and  $n$  has a constant value of 2.5 for human blood; in other words, if a fresh series of points is determined, using a different CO<sub>2</sub> pressure, they are found to lie on a similar curve, but in this case the value of  $K$  is different;  $K$  diminishes as the CO<sub>2</sub> pressure is increased, i.e. as the acidity is increased.  $K$  is a constant for this curve, but has different values if acid or alkali is added to the blood.

Now the standard CO<sub>2</sub> pressure usually employed is that of the alveolar air, which is in equilibrium with the CO<sub>2</sub> in the arterial blood, and the resulting curve for any individual usually remains the same from year to year. There is at least one notable exception to this, viz. Higgins, where the blood had definitely altered on the second occasion on which it was tested (see Table V). However, it may be said that the value of  $K$  at alveolar CO<sub>2</sub> pressure is usually constant for the individual; but there are alterations in the value of  $K$  for different individuals.

It has been shown by Barcroft and others that the value of  $K$  in the individual still remains constant in cases of acidosis where there is an increase of some fixed acid in the blood. In this connexion the term acidosis is used in its widest sense to include the presence of any acid in the blood not present in the normal individual during rest. It is not restricted to the presence of aceto-acetic and  $\beta$ -oxybutyric acids, though the presence of these acids is, of course, included in the term. If a single word implying the formation of these bodies in metabolism is required, the term 'ketosis' would seem to be a very suitable one for the purpose.

It has been known for long, i.e. since Beddard, Pembrey, and Spriggs' paper (16), that many states of acidosis were associated with lowering of the alveolar CO<sub>2</sub> and consequently of the arterial CO<sub>2</sub> pressure. From the fact that  $K$  remained constant (15) it was argued that the lowering of the CO<sub>2</sub> pressure

was compensatory to the increase of fixed acid in the blood, so that the reaction of the blood, i.e. its acidity or alkalinity, or, more satisfactorily expressed, its hydrogen ion concentration, remained unaltered. Such states of acidosis included the ketosis obtained with a diet restricted to protein and fat, and the acidosis observed at high altitudes.

This constancy in blood reaction under different conditions of diet was proved definitely by Hasselbalch (17), by means of actual determinations of the hydrogen ion concentration. Hence it seemed probable that  $K$  was related in some manner to the hydrogen ion concentration of the blood.

Peters (15) worked out this relationship with Barcroft's blood as follows: Barcroft and Poulton (18) had determined the value of the  $K$  for Barcroft's blood, not only at the normal alveolar  $\text{CO}_2$  pressure, but at other pressures of  $\text{CO}_2$ . They constructed a curve, which is shown in Fig. 1, in which the values for  $\log K$  are plotted against the  $\text{CO}_2$  pressures in mm. Peters, by direct determinations of the hydrogen ion concentration of Barcroft's blood, also at varying  $\text{CO}_2$  pressures, obtained a curve representing the relation between the values of  $ph$  (the exponent of the hydrogen ion concentration) and of the  $\text{CO}_2$  pressure in mm. From these two sets of figures corresponding values of  $\log K$  and  $ph$  can be plotted against one another, and the resulting curve was found to be a straight line, which has been called by Hasselbalch the Peter-Barcroft curve. Hasselbalch (19) found that in several normal individuals the relation between the  $\log K$  and  $ph$  was also expressed by the same curve. However, there is evidence that in other cases where the  $K$  is abnormally low this relationship does not hold; but it is at present uncertain what other factor is involved in these cases.

As the value of  $\log K$  corresponding to the alveolar  $\text{CO}_2$  pressure is usually constant for the individual, it seems worth while to publish our results on eleven normal men carried out in 1915, even though their exact significance may be uncertain at present. Our results are shown in Table V, indicated by the letters A-K, and they have been incorporated with thirteen other cases from the literature. In this table the results are placed in order corresponding to decreasing values of  $K$ , i.e. the acidity of the blood measured at alveolar  $\text{CO}_2$  pressure increases on descending the table. In order to get an indication of the distribution of these results, they have been separated into groups I-VI by horizontal lines, which are drawn to represent values of  $K$  (as shown in the table) differing from one another by 0.00003.

Of these twenty-four results, fourteen fell within the middle two groups, III and IV. The middle terms of the whole series are 0.000218 and 0.000200, while the arithmetic mean is 0.000282. No relation exists between the alveolar  $\text{CO}_2$  (see column 2) and the corresponding value for  $K$ .



TABLE V.

*Normal Oxy-haemoglobin Dissociation Curves in Blood.*

Subject.	Alv. CO <sub>2</sub> . mm.	K.	Group.
H	33.3	0.000366	I
Ryffel	44.4	0.000363	
			0.00035
Roberts	39.0	0.000330	II
			0.00032
Graham	41.0	0.000317	III
J	45.5	0.000316	
K	38.2	0.000316	
Camis	40.0	0.000315	
C	41.0	0.000309	
Higgins (1)	38.0	0.000301	
Barcroft	40.0	0.000292	
G	40.4	0.000291	
			0.00029
R. O. G. Convalescent. Operation for appendicitis	36.2	0.000280	IV
D	39.3	0.000278	
E	41.7	0.000278	
A	40.3	0.000275	
H. H. Convalescent. Gastric symp- toms	38.7	0.000270	
Higgins (2)	38.0	0.000264	
			0.00026
W. S. Convalescent. Operation for fistula	40.3	0.000250	V
I	43.8	0.000246	
F	44.4	0.000237	
B	39.9	0.000230	
			0.000230
Douglas	41.0	0.000212	VI
Haldane	40.0	0.000212	
Mathison	39.0	0.000212	
	Mean	0.000282	

*The Buffer Value of Normal Blood.*

The word 'buffer' is applied to those substances in a solution that tend to lessen the alteration in hydrogen ion concentration, when acid or alkali is added to the solution.

Levy and Rowntree (24) have estimated the 'buffer value' of blood after dialysis by the use of indicators. There are not many observations on blood carried out as far as possible under physiological conditions. The method that has been employed by Hasselbalch (19), Barcroft and Poulton (18), Peters (15), Parsons (20), and others, is to measure the *ph* directly, or the log *K* of Hill's formula at varying pressures of CO<sub>2</sub>. In other cases the volume of CO<sub>2</sub> dissolved in 100 c.c. of blood has been measured, and the relation between this quantity and the log *K* or *ph* has been determined.

Hasselbalch (19) has shown, as has already been stated, that in a number of normal individuals the value of *ph* always corresponds to the same value of log *K* (i.e. the points fall on the P.-B. curve); but he has pointed out that this

is probably not the case in those people whose value for  $K$  is much below the average (e.g. the  $K$  for Haldane, Table V). Still, even in these cases, the change in  $\log K$  and the change in  $ph$ , produced by the addition of acid, is always the same, so that the change in  $\log K$  can be used to determine the 'buffer value' of blood in normal people.

In our determinations defibrinated blood was used, the blood being kept on ice before the experiment. 3 c.c. of blood were placed in a tonometer containing a known pressure of  $O_2$  and  $CO_2$ . After saturating in a water-bath at  $37^\circ C$ , 1 c.c. of blood was delivered beneath dilute ammonia into each of two Barcroft's differential blood-gas apparatuses. Hence, for each pressure of  $CO_2$ , duplicate values for  $\log K$  were obtained, and the mean values are given in Table VI. When the value of  $CO_2$  was determined, care was taken to see that the ammonia contained no  $CO_2$ . It was found that the stock-bottle of liquor ammonia, which was often renewed for class purposes, contained no appreciable quantity of  $CO_2$  when tested chemically, or by the differential apparatus. The necessary dilution was carried out just before the experiment. After the oxygen had been driven off, tartaric acid was admitted and the  $CO_2$  was liberated. On several occasions blank experiments showed that the effect of the tartaric acid in neutralizing the ammonia, and so eliminating the pressure of ammonia vapour, did not produce an appreciable alteration in the level of the clove oil, and so was negligible. Care was taken to arrange the oxygen pressure so that the saturation of the blood with oxygen always lay between 40 per cent. and 60 per cent. By this means the error pointed out by Christiansen, Douglas, and Haldane, due to reduced haemoglobin taking up more  $CO_2$  than oxyhaemoglobin, was avoided. Barcroft and Haldane's correction (22) was applied to allow for the solubility of the  $CO_2$  in the fluid from which it was being shaken. The method of calculating the volume of  $CO_2$  from the reading was unusual. The amount of blood delivered from the tonometer was not measured accurately. The volume of  $CO_2$  per 100 c.c. of blood was calculated from the reading of the oxygen and from the haemoglobin content of the blood, as measured by a Haldane's haemoglobinometer, previously standardized by means of the blood-gas apparatus (15, p. 295). The calculation is as follows:

$$V_{O_2} = KR_{O_2},$$

$$V_{CO_2} = KR_{CO_2}; \therefore V_{CO_2} = \frac{R_{CO_2}}{R_{O_2}} x V_{O_2},$$

where  $K$  is the constant of the apparatus and  $V$  and  $R$  are the volumes and readings of the corresponding gases.

Let  $Q$  = volume of blood used, then volume of  $CO_2$  in 100 c.c. blood

$$= \frac{100 V_{CO_2}}{Q} = \frac{100 V_{O_2}}{Q} \times \frac{R_{CO_2}}{R_{O_2}}.$$

Supposing, from the haemoglobinometer reading, 100 c.c. of blood contain  $x$  c.c.  $O_2$ . Then  $Q$  c.c. contain  $\frac{xQ}{100}$  c.c. oxygen, i.e.  $V_{O_2} = \frac{xQ}{100}$ ;  $\therefore$  vol. of  $CO_2$  in 100 c.c. blood =  $x \times \frac{R_{CO_2}}{R_{O_2}}$ .

The advantage of this method is that it is unnecessary to know either the quantity of blood used or the constant of the apparatus, or if these factors are known and used in calculation, our method serves as a useful check on either the oxygen or the  $CO_2$  reading.

The alteration in buffer value of Barcroft's blood was determined by

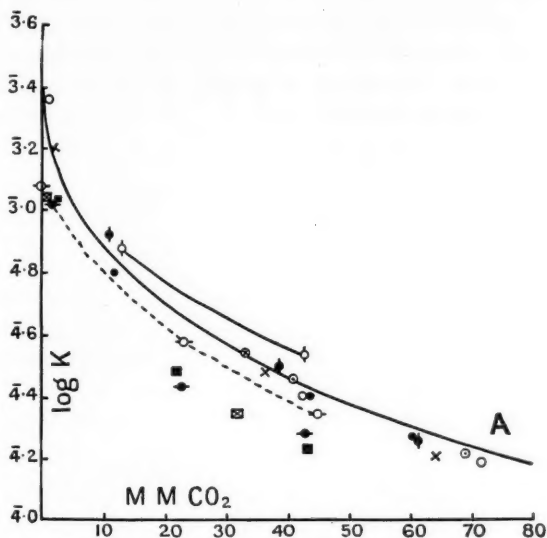
Barcroft and Poulton, who measured this alteration in  $\log K$  with different pressures of  $\text{CO}_2$ . Curve A (Fig. 1) gives their results. We have tested this curve in the case of nine normal men. The results are shown in the figure, and are, roughly, all those above the dotted line. The points for L. S. D. are not included; the  $K$  in this case was abnormally low. It is evident that these results are distributed pretty evenly on both sides of Barcroft's curve, though with the higher values of  $\text{CO}_2$  the mean of our results is below the curve.

TABLE VI.

		$\text{CO}_2$ mm.	$\log K$ .	$\text{CO}_2$ c.c. in 100 c.c. blood.	Remarks.
D	×	1.9	$\bar{3}.21$		Normal defibrinated blood
		36.4	$\bar{4}.47$		"
		64.3	$\bar{4}.20$		"
E	○	41.3	$\bar{4}.45$		"
		68.6	$\bar{4}.21$		"
F	○	1.4	$\bar{3}.36$		"
		42.4	$\bar{4}.39$		"
		71.5	$\bar{4}.18$		"
H	⊗	33.4	$\bar{4}.56$		"
		1.0	$\bar{3}.02$		+ 0.05 % lactic acid
		32.2	$\bar{4}.34$		"
I.	.	11.4	$\bar{4}.80$		Normal blood
		43.5	$\bar{4}.40$		"
		60.7	$\bar{4}.27$		"
	■	2.3	$\bar{3}.03$		+ 0.05 % lactic acid
		22.1	$\bar{4}.48$		"
		43.6	$\bar{4}.23$		"
J	○	13.0	$\bar{4}.87$	29.6	Normal blood
		43.1	$\bar{4}.53$	49.1	"
	-○-	0	$\bar{3}.08$	11.1	+ 0.05 % lactic acid
		23.3	$\bar{4}.57$	34.9	"
		44.8	$\bar{4}.34$	44.0	"
K	●	11.1	$\bar{4}.92$	26.0	Normal blood
		38.9	$\bar{4}.49$	48.5	"
		61.2	$\bar{4}.25$	63.7	"
	●	1.7	$\bar{3}.02$	6.7	+ 0.05 % lactic acid
		23.1	$\bar{4}.43$	30.2	"
		43.2	$\bar{4}.27$	42.3	"
L. S. D.	○	12.9	$\bar{4}.70$	32.6	Normal blood
		28.2	$\bar{4}.43$	46.6	"
	□	1.8	$\bar{4}.89$	12.5	+ 0.05 % lactic acid
		12.2	$\bar{4}.67$	26.3	"

In three cases we determined the volume of  $\text{CO}_2$  in 100 c.c. blood. These values are plotted against  $\log K$  in Fig. 2 (continuous lines). The buffer value of blood is usually estimated by these curves, rather than by the  $\text{CO}_2$  pressure

curves. It may be expressed by the change in  $\log K$  caused by an addition of 5 c.c. of  $\text{CO}_2$  per 100 c.c. blood. In J and K this value is 0.10, and in the case



A. Curve for Barcroft's blood.

FIG. 1.

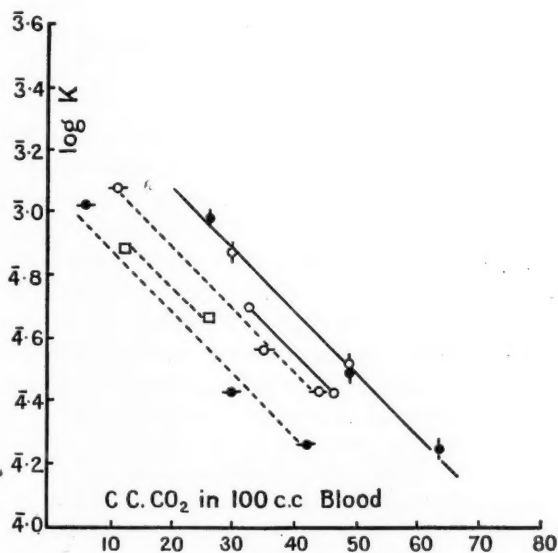


FIG. 2.

of L.S.D. it is 0.095. Parsons (20) has investigated his own blood very completely, and he shows that the points fall on a curve, whereas in Fig. 2 the

points have been joined by straight lines. Over a limited range of volume (i.e. 30 to 50 c.c.  $\text{CO}_2$ ), no great error will result if straight lines are used instead of curves. The buffer value of Parsons's reduced blood is 0.11 with this notation, using the P.-B. curve as explained later. Hasselbalch's results on himself and on four women some days after child-birth give values 0.100, 0.145, 0.133, 0.100, and 0.110. The mean of all these results is 0.11, the maximum being 0.145, and the minimum 0.095.

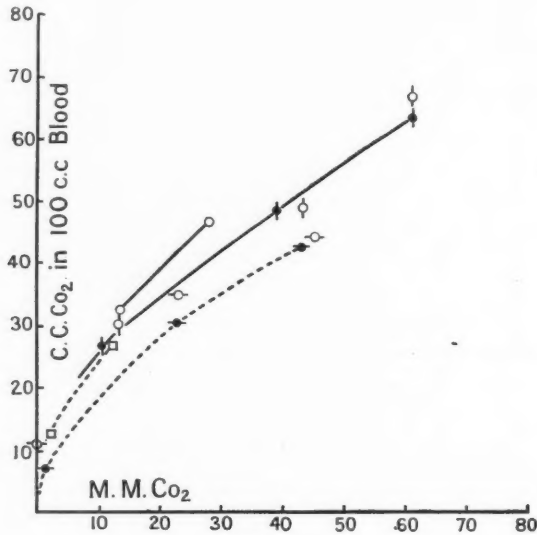


FIG. 3.

Lewis, Cotton, Barcroft, Milroy, Dufton, and Parsons (23) have stated that in cases of irritable heart in soldiers the buffer value of the blood is diminished. The buffer value is given in terms of  $ph$ , but by using the Peters-Barcroft curve their values can readily be converted into  $\log K$ , which was the measurement actually made. By this means their normals are found to be 0.053, 0.081, 0.059, 0.060, which are very decidedly lower than those just given, determined by three independent workers. Further, the buffer values in their cases of irritable heart are 0.183, 0.120, 0.150, 0.120, and 0.101. Only two of them fall outside the normal series given in this paper. Hence, for the present it cannot be said that the lower buffer value of the blood in irritable heart is by any means certain.

#### *The Buffer Value of the Blood in Acidosis.*

In a number of different states of acidosis data have been published by Barcroft and others which can be used for determining the buffer value of the blood in these conditions, by means of the  $\text{CO}_2$  pressure curve.



## RESPIRATION AND OXYHAEMOGLOBIN DISSOCIATION CURVES 57

In the acidosis due to altitude, to exercise at an altitude, and in cases of cardio-renal disease (15), the values of  $\log K$  are given at a certain  $\text{CO}_2$  pressure, usually the alveolar  $\text{CO}_2$  pressure, but in addition the percentage saturation of the oxyhaemoglobin at 17 mm.  $\text{O}_2$ , in the absence of  $\text{CO}_2$ , has been determined, and from this the corresponding  $\log K$  can be calculated. If the alteration in  $\log K$  for a given alteration in pressure is compared in these cases with normal blood, the result, surprising at first sight, is obtained that it requires a smaller increase in  $\text{CO}_2$  pressure to effect a given alteration in  $\log K$  than it does with normal blood.

In trying to explain this, we added 0.05 per cent. lactic acid to some of our normal bloods. The results are shown in Fig. 1 grouped about and below the dotted line. Exactly the same behaviour is observed. Taking Case I as an example (Table VI), in the normal blood it would require an addition of 32 mm.  $\text{CO}_2$  to shift the  $\log K$  from 3.36 to 4.72; in the lactic acid blood it would require only 20 mm.

In three cases we made a simultaneous determination of the volume of  $\text{CO}_2$  (see Fig. 2) in the acid blood. The dotted lines are drawn, intentionally, exactly parallel to the corresponding lines for the normal bloods. Practically speaking, the dots fall on these lines, which means that the same volume of  $\text{CO}_2$  is required in these two cases for a given alteration in  $\log K$ . In other words, the buffer value of the blood measured in this way is not perceptibly altered if acid is added to it. The same result has been found by Parsons (20), in comparing the buffer value of his fully oxidized blood and fully reduced blood. The importance of this result will be obvious when the problem of breathlessness in patients with acidosis is considered.

The explanation of the different behaviour of the  $\text{CO}_2$  pressure is given by Fig. 3, in which the  $\text{CO}_2$  content of the blood is plotted against the  $\text{CO}_2$  pressure. In both the normal and the acid blood the volume of  $\text{CO}_2$  at 0 mm.  $\text{CO}_2$  pressure is nil. With a small addition of  $\text{CO}_2$  to the atmosphere there is a much more rapid increase of  $\text{CO}_2$  in the normal blood than there is in the acid blood, and the difference between the two becomes steadily less as the pressure rises. Hence it is not surprising that the hydrogen ion concentration, or the  $\log K$ , should increase more rapidly in the normal than in the acid blood.

There is one point that is not very easy to explain. In all our cases of acid blood, 0.05 per cent. lactic acid was added. The requisite volume of a 10 per cent. solution was carefully weighed out and added to the blood, which was immediately mixed. The effect of adding this lactic was very different in the three cases, as shown by Fig. 2. It was large in the case of K, and small in the case of L. S. D., and yet the buffer value as measured by the  $\text{CO}_2$  was much the same in all three cases.

TABLE

Subject. Age. Wt. in kilos.	Nature of case.	Pulmonary Ventila- tion (litres per min. at 37° C. and pre- vailing at- mospheric pressure saturated with moisture).	Alveolar Ventila- tion (litres per min. at 37° C. and pre- vailing at- mospheric pressure saturated with moisture).	No. of Respira- tions per min.	Tidal Air. c.c. measured moist at 37° C. and prevailing atmo- spheric pressure.	Tidal Alveolar Air. c.c. measured moist at 37° C. and prevailing atmo- spheric pressure.	Dead Space. c.c.	Dead Space of Mask. c.c.
A	Crushed fingers. Operation 5 days pre- viously	5.438	3.348	11.9	457	281	126	50
34		4.657	2.934	11.8	394	249	96	
62.2	(Mean)	5.048	3.141	11.85	426	265	111	
B	Fractured femur	6.190	3.420	18.0	344	190	114	40
38		5.810	3.423	15.6	373	220	113	
61.1	(Mean)	6.000	3.426	16.8	359	205	114	
C	Fractured femur	6.996	4.128	21.0	333	197	99	About 38
19		5.976	3.723	19.6	305	190	77	
58.2	(Mean)	6.486	3.926	20.3	319	194	88	
D	Fractured tibia	7.270	4.467	19.2	379	233	111	35
22								
55.6								
E	Cut external popliteal nerve	6.360	4.534	14.2	448	319	96	32
49		5.987	4.424	13.4	448	330	85	
78.3	(Mean)	6.174	4.479	13.8	448	325	91	
F	Abscess on tibia	5.487	3.644	14.8	371	246	90	32
28		5.424	3.640	14.2	382	256	91	
54.2	(Mean)	5.456	3.642	14.5	377	251	91	
G	Fractured tibia	6.276	4.139	15.6	402	265	104	33
28		6.203		17.2	351			
54.2	(Mean)	6.240		16.4	332			
H	Flatfoot	7.620	5.670	13.7	555	414	109	33
18		7.470	5.380	15.2	491	354	105	
55	(Mean)	7.550	5.525	14.45	524	334	107	
I	Traumatic Cataract	5.990	3.935	12.3	487	320	136	31
22		5.016	3.596	10.1	497	356	110	
—	(Mean)	5.503	3.766	11.2	492	338	123	
J	Traumatic Cataract	4.951	3.131	12.4	399	253	116	31
32		4.791	2.993	12.3	390	243	115	
—	(Mean)	4.871	3.062	12.35	395	249	116	
K								
<i>Mean of all results</i>		6.06	3.94	15.1	410	271	105.4	

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## VII.

Al- veolar CO <sub>2</sub> pres- sure. mm.	Respiratory Exchange.				R. Q. (cor- rected).	Oxygen Dissociation Curves in Blood.				K cal- culated for pres- sure of alveolar CO <sub>2</sub> .
	CO <sub>2</sub> . c.c. per min. at 0° C. and 760 mm.	O <sub>2</sub> . c.c. per min. at 0° C. and 760 mm.	CO <sub>2</sub> . c.c. per kilo per min. at 0° C. and 760 mm.	O <sub>2</sub> . c.c. per kilo per min. at 0° C. and 760 mm.		CO <sub>2</sub> . mm.	O <sub>2</sub> . mm.	% Satura- tion.	K.	
40.3	155	229	2.49	3.69	0.676	34.8	26.9	51.2	0.000278	
	136	214	2.19	3.44	0.634	37.8	27.0	56.1	0.000336	
	146	222	2.34	3.57	0.654	36.3	27.0	53.6	0.000306	0.000275
39.9	158	211	2.58	3.46	0.747	38.7	30.2	30.2	0.000236	
	158	215	2.58	3.51	0.737			30.2	0.000236	
	158	213	2.58	3.49	0.742			30.2	0.000236	0.000230
41.0	195	259	3.35	4.45	0.751	37.7	27.2	55.6	0.000325	
	176	251	3.02	4.32	0.699			57.4	0.000351	
	186	255	3.19	4.39	0.725			56.5	0.000337	0.000309
39.3	205	232	3.71	4.2	0.883	36.4	23.6	44.3	0.000294	0.000278
41.7	218	243	2.78	3.10	0.899	41.3	29.1	57.2	0.000293	
	213	251	2.72	3.21	0.848			55.1	0.000269	
	216	247	2.75	3.16	0.874			56.2	0.000280	0.000278
44.4	186	236	2.52	3.20	0.771	42.4	21.9	35.5	0.000244	0.000237
	186	219	2.52	2.96	0.852					
	186	228	2.52	3.08	0.802					
40.4	192	220	3.47	3.97	0.874	41.3	29.5	58.2	0.000294	
								57.1	0.000281	
								57.7	0.000287	0.000291
38.3	218	274	3.97	4.98	0.797	33.4	36.4	75.2	0.000379	
	207	262	3.77	4.77	0.790			73.9	0.000354	
	213	268	3.87	4.88	0.794			74.6	0.000366	0.000366
43.8	199	228			0.873	43.5	32.2	57.8	0.000233	
	181	254			0.713			61.0	0.000266	
	190	241			0.793			59.4	0.000249	0.000246
45.5	163	193			0.843	43.1	29.1	58.4	0.000308	
	156	191			0.816			63.2	0.000377	
	160	192			0.830			60.8	0.000340	0.000316
38.2						38.9	28	59.8	0.000359	
								53.0	0.000272	
					(Mean)			56.4	0.000312	0.000316
40.7	185	232	3.05	3.84	0.797					0.000286

*Summary.*

1. The pulmonary ventilation, alveolar  $\text{CO}_2$ , alveolar ventilation, tidal air, dead space, and respiratory exchange have been measured in ten normal men at rest in bed.
2. The methods described by Haldane and Priestley, and by Hasselbalch and Lindhard, for measuring the alveolar  $\text{CO}_2$  have been compared, and show satisfactory agreement.
3. Values for  $K$  (the constant of the oxyhaemoglobin dissociation curve) at the alveolar  $\text{CO}_2$  pressure have been determined in eleven normal men, and agree with values previously published.
4. Results for the buffer value of normal blood are given.
5. The buffer value of blood in states of acidosis is considered.

## REFERENCES.

1. Hasselbalch and Lindhard, *Skand. Arch. f. Physiol.*, 1911, xxv. 361.
2. Haldane and Priestley, *Journ. Physiol.*, Camb., 1905, xxxii. 225.
3. Krogh, *The Respiratory Exchange of Animals and Man*, Lond., 1916.
4. Benedict, Emmes, and Riche, *Amer. Journ. Physiol.*, 1910-11, xxvii. 383.
5. Pembrey and Schlesinger, *Journ. Physiol.*, Camb. (Proc.), 1908, xxxvii. 69.
6. Douglas, Haldane, Hobson, and Campbell, *ibid.*, 1913, xli. 301.
7. Boothby and Peabody, *Arch. Int. Med.*, Chicago, 1914, xiii. 497.
8. Plesch, *Zeitschr. f. exp. Path. u. Ther.*, Berlin, 1909, vi. 380.
9. Krogh and Lindhard, *Journ. Physiol.*, Camb., 1917, li. 59.
10. Haldane, *Amer. Journ. Physiol.*, 1915, xxxviii. 20.
11. Henderson, Chillingworth, and Whitney, *ibid.*, 1915, xxxviii. 1.
12. Pearce, *ibid.*, 1917, xli. 369.
13. Lindhard, *Journ. Physiol.*, Camb. (Proc.), 1914, xlviii. 44.
14. Loewy, *Pflüger's Archiv f. d. ges. Physiol.*, Bonn, 1894, lviii. 416.
15. Barcroft, *The Respiratory Function of the Blood*, Camb., 1914.
16. Beddard, Pembrey, and Spriggs, *Journ. Physiol.*, Camb. (Proc.), 1908, xxxvii. 39.
17. Hasselbalch, *Biochem. Zeitschr.*, Berlin, 1912, xli. 403.
18. Barcroft and Poulton, *Journ. Physiol.*, Camb. (Proc.), 1913, xli. 4.
19. Hasselbalch, *Biochem. Zeitschr.*, Berlin, 1917, lxxxii. 282.
20. Parsons, *Journ. Physiol.*, Camb., 1917, li. 440.
21. Christiansen, Douglas, and Haldane, *ibid.*, 1914, xlviii. 244.
22. Barcroft and Haldane, *ibid.*, 1902, xxviii. 232.
23. Lewis, Cotton, Barcroft, Milroy, Dufton, and Parsons, *Brit. Med. Journ.*, 1916, ii. 517.
24. Levy and Rowntree, *Arch. Int. Med.*, Chicago, 1916, xvii. 525.

## SOME OBSERVATIONS UPON CASES OF VOMITING IN PREGNANCY

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A LARGE amount of investigation by laboratory methods has been devoted to the pathology of pernicious vomiting and the allied disorders of pregnancy; and it must be admitted that the results, which have been discussed by Ewing (1, 2), Underhill and Rand (3), Leathes (4), Losee and van Slyke (5), and others, fail to give any clear picture of the nature of these conditions. Very extensive observations, involving analyses of numerous constituents of the urine and examination of the blood and expired air, are required in order to throw much new light on this subject; even the elaborate work of Losee and van Slyke omits some very desirable data. The present communication serves to record three cases in which the examination of the urine was found to be of some empirical value; moreover, the number of cases in the literature in which daily analyses were made for any length of time is extremely small, so that some addition to their number seems justified.

The term 'ammonia index' in this paper denotes the amount of ammonia nitrogen of the urine reckoned as a percentage of the total nitrogen. This seems to be the best term to employ; 'ammonia percentage' would be ambiguous; the word 'coefficient' is often used, but is not very suitable for a percentage.

*Case I.* (See Table I and Fig. 1.) P. S., Jewess, aged 31, admitted on 15.6.16 under the care of Mr. Comyns Berkeley for severe vomiting of pregnancy. Her last menstrual period ended on 4.5.16 and the vomiting began on 26.5.16.

The previous history is unusual and striking; this is the patient's fifth pregnancy, and during each vomiting has been excessive.

- Pregnancy 1. Labour at the seventh month. She vomited throughout the pregnancy.
- " 2. Miscarriage at ten weeks. She vomited all the time.
  - " 3. Full term delivery. Vomiting slight.
  - " 4. Miscarriage at eighth week, very bad vomiting all the time.
  - " 5. Present pregnancy, the vomiting began twenty-two days after the cessation of menstruation and before the patient had missed a period. She was admitted to hospital after vomiting for three weeks.

On admission she vomited after any attempt to take by mouth, even fluids, and on examination the uterus was found to be enlarged and softened.



The patient was given every 4 hours rectal injections of saline containing bicarbonate of soda gr. 20 and dextrose gr. 60. In spite of this treatment the vomiting persisted and the ammonia index of the urine increased very rapidly (see Table I), and her uterus was emptied by one of us (W. G.) four days after admission. A small foetus, about 1 inch in length, showing limb buds was removed.

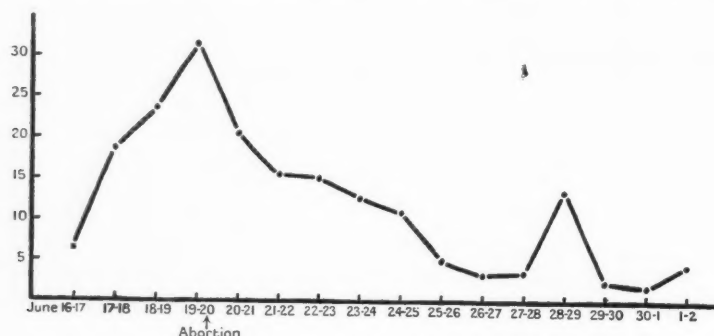


FIG. 1. Case I. Ordinates represent ammonia index.

TABLE I. Case I.

	Total Nitrogen. mg. %.	Am- monia Nitrogen. mg. %.	Am- monia Nitrogen. % of Total Nitrogen.	Acidity. N c.c. $\frac{N}{10}$ %.	Tests for Aceto-acetic Acid.	
					FeCl <sub>3</sub> .	Rothera.
June 16	1,400	91	6.5	67.6	++	quick-strong *
" 17	1,178	223	18.9	59.0	++++	"
" 18	896	212	23.7	45.2	++++	"
" 19	680	219	31.1	42.8	++++	"
Uterus emptied 20th, 4 p.m.						
" 20-21	1,366	283	20.5	38.2	++++	"
Urine of first 24 hours after abortion						
" 21-22	1,795	280	15.6	25.2	+	slow-strong *
" 22	714	108	15.1	6.8	weak+	"
" 23	574	73	12.7	4.4	0	0
" 24	926	102	11.0	32.8		0
" 25	627	31.6	5.0	13.6		0
" 26	546	17.4	3.2	3.6		0
" 27	376	14.3	3.8	5.2		0
" 28	736	98.5	13.4	14.2	trace	slow-strong
" 29	620	16.1	2.6	6.0	0	0
" 30	674	13.4	2.0	4.2		0

\* See note at end of this paper.

A sample of urine examined the day after admission (June 16) gave a strong ferric chloride reaction for aceto-acetic acid, but the ammonia index was found to be only 6.5 (Fig. 1), which is not significantly above the upper limit of the figures regarded as normal (3 per cent. to 5 per cent.); some discussion of this state of the urine is given later in the paper (see under (2) below). Unfortunately the time available did not admit of the quantitative estimation of the acetone bodies. During the next three days the ferric chloride reaction became maximal, i. e. the

fluid had the well-known black appearance by reflected light, and the ammonia index rose from 6.5 to 31.1.

Following the operation, the patient improved very rapidly, and the vomiting ceased entirely within twelve hours of the uterus being emptied.

On the day after the abortion the ammonia index had fallen from 31.1 to 20.5, and subsequently it fell at a fairly uniform rate to within normal limits (5 per cent.) on the sixth day (June 26). The aceto-acetic acid disappeared very rapidly, both the ferric chloride and nitroprusside (Rothera's) tests<sup>1</sup> being negative on the fourth day. The beneficial effect of the operation was therefore very distinct both from the clinical and chemical aspects. On the ninth day (June 28), when the ammonia had been for three days within normal limits, some surprise was occasioned by the sudden appearance of strong Rothera and weak ferric chloride reactions, and by the rise of the ammonia index from 3.8 to 13.4. On inquiry, nothing could be found to account for this change, except that the patient had felt unwell, and had suffered from toothache; there had been no vomiting. This temporary acidosis was not due to any restriction in the supply of carbohydrate, for the patient had been for some days on ordinary diet, and had eaten on the day in question the usual amounts of bread, potatoes, and fruit; this does not of course exclude the possibility of some failure in the digestion of carbohydrate, such as is very apt to occur in children on admission to hospital (Frew (6)) in spite of an ample supply of carbohydrate food. On the following day the aceto-acetic acid had disappeared and the ammonia index had returned to the normal level.

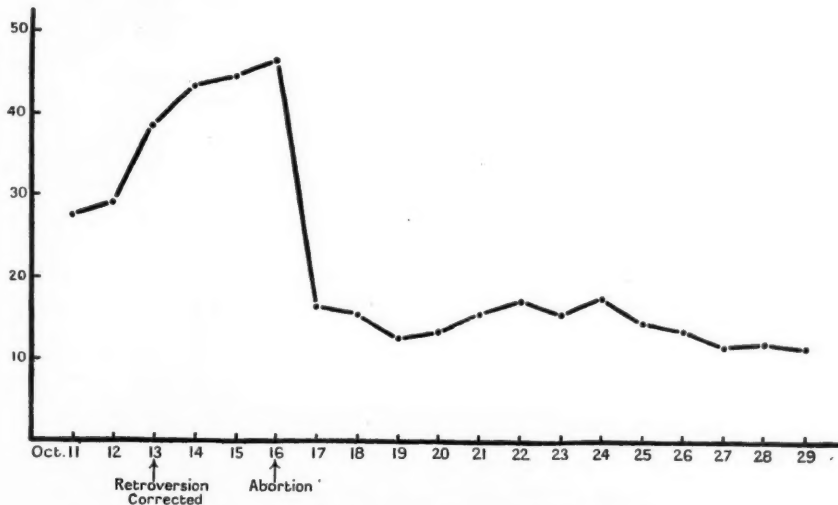


FIG. 2. Case II. Ordinates represent ammonia index.

*Case II.* (See Table II and Fig. 2.) V. N., Jewess, aged 22, admitted to a medical ward on 9.10.16 and came under the care of Mr. Comyns Berkeley on 13.10.16 for severe vomiting of pregnancy. Her last menstrual period ended on August 10, and the vomiting began on September 16. Her previous history is interesting. This is her fifth pregnancy, the first three ended at full term, and during each she suffered from vomiting between the second and fourth months, but not very markedly in excess of normal; her fourth pregnancy had to be ended at the ninth week for persistent and intractable vomiting.

<sup>1</sup> See note at end of this paper.

In the present pregnancy she was admitted to hospital when approximately eight weeks pregnant and after the vomiting had been present for three weeks.

On admission she vomited after every attempt to take anything by mouth, and was given every four hours rectal injections of saline containing 10 per cent. of dextrose. As the vomiting persisted and the ammonia index of the urine rose steadily she was transferred to the gynaecological ward and found to have a retroverted gravid uterus, which was replaced. This had no effect on the vomiting or the urine, and the uterus was emptied on 16.10.16.

On the day after operation the patient was much better and able to retain fluids given by mouth; this improvement was steadily maintained.

TABLE II. *Case II.*

	Volume.* c.c.	Total Nitrogen.		Ammonia Nitrogen.		Ammonia Nitrogen. % of Total Nitrogen.	Acetone + Aceto-acetic Acid as Aceto-acetic Acid.		Acidity. c.c. $\frac{N}{10}$ %	
		mg. %.	gm. per day.	mg. %.	gm. per day.		mg. %.	gm. per day.		
Oct.										
11-12	680	1,229	8.35	336	2.29	27.3	493	3.35	40.0	
12-13	(350)	966		280		29.0	501		32.0	
13-14	(400)	532		204		38.3	353		25.8	Retroversion corrected 13th
14-15	830	664	5.51	287	2.38	43.3	557	4.62	40.0	
15-16	840	728	6.11	322	2.71	44.3	663	5.57	40.0	
16-17	(660)	654		302		46.2	578		32.8	Uterus emptied 16th, 4 p.m.
17-18	(380)	896		149		16.7	133		17.8	
18-19	690	1,040	7.17	161	1.11	15.5	198	1.36	11.2	
19-20	(490)	865		110		12.7	65		6.2	
20-21	(1,030)	497		67		13.5	14.4		4.0	
21-22	(1,125)	343		53		15.3	7.5		2.4	
22-23	(320)	435		74		17.1	trace		5.8	
23-24	(270)	740		112		15.2	0		6.0	
24-25	(540)	560		98		17.5	0		7.6	
25-26	(495)	364		52		14.3	0		4.0	
26-27	(600)	554		74		13.3	0		7.0	
27-28	670	672	4.50	79	0.529	11.7	0		5.8	
28-29	890	546	4.86	66	0.587	12.0	0		6.3	
29-30	890	465	4.14	49	0.436	10.6	0		7.0	
Nov.										
5 & 6	(2,400)	592		66		11.2	0		5.0	Urine collected over more than 24 hours

\* Brackets indicate that complete 24 hours' amount could not be obtained.

The urine of the first twenty-four hours after admission showed already a high ammonia index (27.3) and a considerable amount of aceto-acetic acid (3.3 gm. per day). During the next five days the ammonia index rose to 46.2 (Fig. 2), the replacement of the retroverted uterus on the third day having no beneficial effect. The total amount of ammonia nitrogen reached 2.7 gm. in a day, whereas under normal conditions the output is seldom as much as 1 gm. The amount of aceto-acetic acid was 5.6 gm. on the day before the abortion; this is a remarkable figure, being as much as is seen in most cases of severe diabetes, in which disease an output of over 10 gm. per day is exceptional; nevertheless the excretion of aceto-acetic acid had ceased completely a week after the abortion. No improvement having followed the correction of retroversion, the uterus was emptied on the sixth day after admission. The effect of the operation on the proportion of ammonia was immediate, the index falling from 46.2 to 16.7 in twenty-four hours; the figure remained above 10 throughout the remainder

of the patient's stay in hospital, but this does not indicate any abnormal state of metabolism; any healthy person taking a diet which produced an output of total nitrogen as low as in this case (4 to 5 gm. daily) would show an equally high proportion of ammonia nitrogen (10 to 12 per cent.), this being due not to any absolute increase in ammonia, but to the decrease in urea (Folin (7)).

The urine was coloured with bile pigment throughout the period before the abortion, but none was detected on the next and subsequent days.

The following unusual points may be noted with regard to the two cases detailed above:

(1) Both patients were Hebrew, and the only fatal case of vomiting of pregnancy in the records of the Middlesex Hospital for the last ten years was also a Jewess.

(2) The history of the occurrence of vomiting in previous pregnancies in each patient. In Case I vomiting had been excessive in four out of five pregnancies, and in Case II a previous pregnancy had to be terminated for this condition.

TABLE III. *Case III.*

	Volume. c.c.	Total Nitrogen.		Ammonia Nitrogen.		Ammonia Nitrogen. % of Total Nitrogen.	Acetone + Aceto-acetic Acid as Aceto-acetic Acid.		Acidity. N c.c. $\frac{N}{10}$ %.	
		mg. %.	gm. per day.	mg. %.	gm. per day.		mg. %.	gm. per day.		
Mar. 7-8	not complete	1,120		6.6		0.59			5.4	
8-9	440	916	4.03	4.5	0.0198	0.49	45.2	0.199	5.1	Albumin, dis- tinct. No casts. Urobilin, dis- tinct. Indican +
9-10	600	1,242	7.45	7.0	0.042	0.56	21.7	0.130	6.0	Albumin in- creased. Uro- bilin, not ab- normal. Bile pigment, trace. Indican + + +

*Case III.* (See Table III.) M. M., English, aged 38, admitted to a medical ward on 3.3.17 and came under care of Mr. Comyns Berkeley on 9.3.17. She was a primigravida, six months pregnant, her last menstrual period having occurred in the middle of September 1916. A week before admission patient began to vomit all solid and liquid food; vomit was not blood-stained or dark. Fuller history could not be ascertained as patient was much exhausted and soon became incoherent in talking. Temp. 99°, pulse 108, respirations 28. Uterus reached level of umbilicus. There was visible peristalsis in epigastric region, and patient complained of pain here. Vomiting occurred frequently; the material was dark, of alkaline reaction, and contained blood.

The urine on March 7 gave a fairly strong ferric chloride test for aceto-acetic acid, and 'slow-strong' Rothera reaction; the amount, however, decreased progressively during the next three days, until on the 10th the ferric chloride reaction was barely perceptible, and quantitative estimation showed the day's output of aceto-acetic acid to be only 0.13 gm. (cf. in Case II, 3 to 5 gm. daily).

Such an amount may be produced by a normal person after a single day's fast (see for instance Kennaway (8), Case XIX). This diminution caused some surprise, as the case was at first regarded as one of pernicious vomiting, in which any such change would be unlikely before abortion. Further, the amount of ammonia was found to be, not raised, but much below the normal (0.02 to 0.04 grm. per day, which was only 0.5 per cent. of the total nitrogen; cf. in Case II, 2.7 grm. per day, or 44 per cent. of the total nitrogen); in view of this remarkable result all the reagents employed were checked, but no error was found and results of the usual type were obtained with other urines. The patient was receiving sodium bicarbonate in rectal injections, but such amounts of alkali, which may or may not have been completely absorbed, would be unlikely to cause so great a diminution in ammonia, for the urine was only faintly alkaline to litmus; in the experiments of Sellards (9), in which the urine was rendered distinctly alkaline by administration of sodium bicarbonate, no such diminution is seen. Hasselbalch (14), experimenting upon himself, found that 25 grm. (385 gr.) of sodium bicarbonate daily were required to reduce the ammonia output to from 0.02 to 0.05 grm. per day; the ammonia index was 0.2. Janney (10), in a full investigation of this matter, found that the administration of 15 to 20 grm. (230 to 300 gr.) sodium bicarbonate by the mouth reduced the ammonia nitrogen per day to 0.15 grm., or 1.2 per cent. of the total nitrogen (average of observations on seven persons). In one case (No. 31), by giving over 900 gr. of bicarbonate, the ammonia nitrogen was reduced to 0.0086 grm. per day, or 0.12 per cent. of the total nitrogen; these appear to be the lowest figures recorded in the literature.

The possibility of acute pancreatitis was considered, but the starch-digesting power of the urine was found to be no greater than that of a normal control. The second sample of urine examined (March 9) showed a fairly strong reaction for indican, and on the next day the amount had become greatly increased; this fact, together with the history of gastric trouble, caused the question of intestinal obstruction to be still further considered in the diagnosis, and Mr. Comyns Berkeley decided to open the abdomen. The uterus was of the size usual in a six months' pregnancy and presented no abnormality. The stomach was found to be of typical hour-glass form, the obstruction being due to adhesions. The adhesions were divided, the obstruction relieved, and the wound closed. The patient died about six hours later, the temperature having risen from 98° to 106°. At the autopsy, the observations made on the stomach at the operation were confirmed; the uterus contained a foetus apparently about six months old.

In considering the diagnostic bearing of the examinations of the urine in this case, one must bear in mind (1) that a considerable degree of indicanuria occurs in some cases of pernicious vomiting (Ewing and Wolf (11), Stone (12)); our Cases I and II were not examined in this respect; and (2) that abnormally low figures for the ammonia have been found in certain cases in which the diagnosis of pernicious vomiting was made (Ewing and Wolf, Cases X and XII, ammonia nitrogen 2.6 and 1 per cent. of total nitrogen; Stone, Cases I and II, 1.2 and 2.5 per cent.); but we have found no amounts recorded which are as low as those in our Case III. In this as in many other conditions no single datum obtained by laboratory methods gives a complete solution of the diagnosis.

### *Discussion of Results.*

1. In Case II the sudden attack of acidosis on June 28, though of a very mild character and unaccompanied by vomiting,<sup>2</sup> is of interest in considering the question of the cause of pernicious vomiting. It suggests that these women, who

<sup>2</sup> Recurrences of severe vomiting after abortion, with considerable rise in the ammonia index, occurred in Cases II and III of Whitridge Williams's first series (see under (3) below).



exhibit the disorder repeatedly during pregnancies, are liable to respond by the production of abnormal acids to various disturbing factors, of which pregnancy is not the only one. It would have been interesting to ascertain whether this patient, when not pregnant, required more than the minimum amount of carbohydrate (80 to 100 gm. daily) which is necessary to prevent acetoneuria in a normal person (Satta (13)), but we were not able to keep her sufficiently long under observation. It must be remembered that there is in healthy pregnancy a tendency to produce in slight degree some of the features of pernicious vomiting; some amount of morning sickness is common, and there are indications of acidosis in the diminution of the plasma bicarbonate (Losee and van Slyke (5), see Table X, below) and in the lowered alveolar carbon dioxide and increased ammonia index (Hasselbalch and Gammeltoft (14); see also Hasselbalch (16)). The latter workers, as the result of a very large number of observations upon ten women, found the average ammonia index to be 5.9 during pregnancy and 4.9 after delivery. In one case the following average results were obtained:

TABLE IV.

*Hasselbalch and Gammeltoft.*

	Urine.	
	pH	Ammonia Index.
Pregnancy, 3rd month	5.8	5.1
" 6th month	6.0	6.0
" 9th month	6.2	7.8
After delivery	5.8	4.8

In the same subject the alveolar  $\text{CO}_2$  tension fell during pregnancy from 38 mm. to 30 mm., and returned to 38 mm. after delivery; in eleven women the average rise of alveolar  $\text{CO}_2$  tension after delivery was 7 mm. It seems that no explanation has yet been offered of this state of acidosis during normal pregnancy; one must bear in mind that the mother has to dispose of the acids produced by the foetus, and that the increased lung-ventilation will provide an additional supply of oxygen required for the placental circulation.

2. Much discussion has been devoted to the question whether the high ammonia index seen in pernicious vomiting is due wholly to the attendant starvation. The total amount of ammonia excreted per day is possibly of greater value<sup>3</sup> in judging of the condition of a patient, but in cases of the kind in question it is seldom possible to be assured of complete collection of the day's urine; hence the relative amount only is available. The ammonia index depends upon at least four factors, namely (1) the amount of ammonia available for diversion from the normal formation of urea; this is regulated by the amount of protein ingested and must be inferred from the total amount of

<sup>3</sup> The work of Hasselbalch (16) has shown that the ammonia index is of great value as a measure of acidosis, but his results cannot yet be applied in the consideration of such pathological conditions as are dealt with here.

nitrogen excreted; (2) the amount of acid, produced by normal or abnormal metabolism, which requires to be neutralized; and possibly in pathological conditions: (3) excess (Sellards (17)) or defect in the liberation of ammonia from amino-acids; and (4) failure of the activity of the liver in converting ammonia into urea. This complexity makes it difficult to institute comparisons between the values of the index seen in the published cases of starvation and of pernicious vomiting.

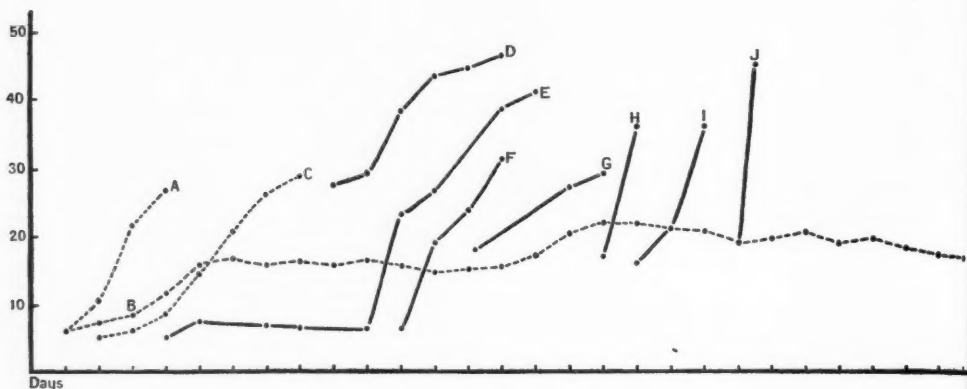


FIG. 3. Rise of Ammonia Index in Fasting and in Pernicious Vomiting.

*Fasting.*

- Curve A. Folin and Denis. Mrs. M.  
B. Benedict.  
C. Bönniger and Mohr.

*Pernicious Vomiting.*

- Curve D. Case II.  
E. Underhill and Rand. Case I.  
F. Case I.  
G. Whitridge Williams, 2nd series, Case I.  
H. Whitridge Williams, 2nd series, Case II.  
I. Whitridge Williams, 1st series, Case III.  
J. Whitridge Williams, 1st series, Case IV (after abortion).

Ordinates represent ammonia index. Abscissae represent days.

In simple starvation (Table V) the ammonia index does not as a rule reach a very high level. In the thirty-one days' fast by a healthy man observed by Benedict (18), the figures show a gradual rise to a maximum of 21.8 on the seventeenth and eighteenth days (Fig. 3), followed by a very slow fall; in the similar fast of fourteen days' duration described by Cathcart (19) the maximum (14.9) is reached on the eighth day; thereafter the figures diminish as in Benedict's case. Brugsch (20) found the index to be over 20 on six of the last eight days of a thirty-one days' fast by Succi, the highest figure being 35.3.

The only observations in the literature upon the effect of prolonged fasting in a healthy woman appear to be those of Bönniger and Mohr (21); unfortunately the value of the figures for the present purpose is affected after the seventh day by the administration of amino-acids (Table V). The changes during these first seven days are very different from those seen in the two men studied by Benedict and Cathcart; the ammonia index mounts rapidly to 28.7 on the

seventh day. One could not in any case generalize from a single instance, but it seems very doubtful whether this indicates any sexual difference in the reaction to starvation. One notes in Bönninger and Mohr's paper (1) that the woman was at the start very well-nourished ('das Fettpolster reichlich entwickelt'); Benedict's and Cathcart's subjects were of distinctly spare build; (2) that the formation of  $\beta$ -oxybutyric acid was very considerable (14.2 gm. on the seventh day); in Benedict's case, in which alone such estimations were made,

TABLE V.

Day of Fast.	Benedict (man).	Cathcart (man).	Brugsch (man).	Bönninger and Mohr (woman).	Folin and Denis.	
					(Mrs. M.)	(Mrs. P.)
1	5.8	3.8			6.0	5.6
2	7.1	4.7		5.3	10.7	5.3
3	8.4	5.3		6.1	21.5	7.2
4	11.8	9.5		8.6	26.6	10.6
5	15.6	—		14.5		
6	16.5	12.6		20.7		
7	15.7	12.6		26.0		
8	16.1	14.9		28.7		
9	15.7	—		20.3 (alanine)		
10	15.8	14.0		17.1		
11	15.4	13.0		17.4		
12	14.7	12.0		17.0		
13	15.0	—		17.8 (leucine)		
14	15.2	9.5		23.4 (glycine)		
15	17.1			28.9		
16	20.2			30.5		
17	21.8					
18	21.8					
19	21.4					
20	20.5					
21	19.8					
22	19.5					
23	20.4		29.5			
24	18.9		23.3			
25	19.4		20.6			
26	18.1		20.4			
27	17.1		25.8			
28	16.9		—			
29	17.5		35.3			
30	16.9		15.4			
31	17.9					

the output did not reach its maximum of one-half this amount until a later date (eighteenth day); and (3) that the total amounts of aceto-acetic and  $\beta$ -oxybutyric acids excreted run roughly parallel to the course of the ammonia index; the same phenomenon is well shown by the results obtained by Folin and Denis (22) during fasts of four days' duration only in two women (Table V). It seems then that the rapid rise of the ammonia index in Bönninger and Mohr's subject was due to the formation of increasingly large amounts of aceto-acetic and  $\beta$ -oxybutyric acid from the store of fat catabolized in the absence of carbohydrate food;<sup>4</sup> the same

<sup>4</sup> Folin and Denis conclude from the valuable data given in the paper quoted above that there is no relation between obesity and the degree of acidosis developed on fasting. This conclusion does not seem to us justified, but a discussion of the point is outside the scope of this paper.

explanation would apply in the case of Mrs. M. (Folin and Denis), in which a quite exceptional quantity of acetone bodies was produced (see under (4) below).

Two other cases of deficient nutrition in women may be mentioned. Nebelthau (23) describes a case of hysterical anorexia and vomiting which had persisted for three years, in which the index reaches 53;<sup>5</sup> but the total nitrogen output was most exceptionally low (between 1.5 and 2.5 grm. daily), this being perhaps due to the long duration of the inadequate feeding, whereby the tissue metabolism was reduced to the lowest possible level. Underhill and Rand (3) record a case of malingering which, if properly investigated, would have provided a very valuable control upon the findings in genuine cases of pernicious vomiting. The patient, who desired the pregnancy to be terminated, refused food, and when alone induced vomiting by putting the fingers into the throat; she had become markedly emaciated. Unfortunately analyses of the total nitrogen and ammonia are given for two days only; the ammonia index was 33 and 22.4. No statement is made as to the excretion of acetone bodies.

When one compares these results from cases of starvation with the observations on at any rate certain types of pernicious vomiting, it is seen that the peculiarity of the latter lies, not only in the absolute value which the figures may reach—for many cases show percentages higher than are ever seen in a healthy fasting person (e.g. 75 per cent. with complete absence of urea, in a case observed by Ewing (1))—but also in the remarkably rapid rate of change which may occur at some stage of the disorder. Some data on this point may be tabulated thus (Table VI),<sup>6</sup> and are shown also in Fig. 3.

TABLE VI.

<i>Pernicious Vomiting.</i>		Rise of Ammonia Index.	Rise per Day.
Present paper	Case I	from 6.5 to 31 in 4 days	6.2
	Case II	from 29 to 46 in 5 days	3.4
Underhill and Rand (3)	Case I	from 6 to 39 in 4 days	8.2
Whitridge Williams (15), 1st series	Case III	from 16 to 35 in 3 days	6.3
	Case IV	from 19 to 45 in 12 hours	52.0
	(after abortion)		
Whitridge Williams (24), 2nd series	Case I	from 18 to 27 in 4 days	2.2
	Case II	from 17 to 36 in 3 days	6.3
<i>Fasting (in Women).</i>			
Folin and Denis (22)	Mrs. M. 1st to 4th day	from 6 to 26 in 4 days	5.0
	Mrs. P. 1st to 4th day	from 5.6 to 10.6 in 4 days	1.2
Bönniger and Mohr (21)	4th to 7th day	from 8.6 to 26 in 4 days	4.2

<sup>5</sup> Several writers who quote this remarkable case give the figure as 66; they have not observed that Nebelthau expresses the results as ammonia and not as ammonia nitrogen.

<sup>6</sup> These are all the cases of pernicious vomiting which we have found in the literature showing the sudden rise in question, and they are admittedly selected for this purpose. Where no such rise is recorded the reason may be (1) that only one analysis was made before the abortion, and hence of course any change could not be followed (Ewing and Wolf, Cases VII,

It seems safe to say that such a large and rapid rise as is shown by some of the cases of vomiting in the table above does not occur in simple starvation of such duration as has been maintained in human subjects; the complete series of analyses by Benedict and Cathcart (Table V) show no such great and sudden changes. Nor does this rise seem to be of the same nature as that which occurred as the initial effect of fasting in the women observed by Bönninger and Mohr, and by Folin and Denis, for in all the cases of vomiting included in the table no food had been retained for periods of from several days to two weeks before the rise occurred, and vomiting of less severe type had persisted for some weeks previous to this stage of practically complete starvation. It is true that Brugsch observed some abrupt changes in the case of Succi, but these are of an up and down character; when such irregularities occur in pernicious vomiting they seem to represent, not the natural course of the disease, but the result of some temporary success in the administration of food (see Underhill and Rand's Case I on dates March 3-6, and Whitridge Williams (24) second series, Case I). In cases of the type in question in which dietetic and medicinal treatment give no relief the course of the figures seems to be, when a certain stage is reached, rapidly and steadily upwards.

This abrupt change deserves some further consideration. Unfortunately opportunities for observations from the very beginning of the affection are unlikely to occur, at any rate among hospital patients, who may not come for treatment until they have suffered considerably from defective nutrition. Nevertheless, although they have so suffered, it is remarkable that the urine may at first show no abnormality as regards the ammonia (see Case I, June 16). But sooner or later after this latent period the sharp rise occurs (Table VI), which seems to indicate some sudden exacerbation of the underlying state, and to be different from the effect of simple starvation. This preliminary period and sudden change is shown very well by Underhill and Rand's Case I (Table VII and Fig. 3), which came under observation at an earlier stage than did either of our cases. Throughout the period represented in the table and for about a week previously, all food was vomited at once; on the last two days some dextrose was given per rectum.

VIII, and IX; Whitridge Williams, first series, Case II), or the analyses were made at too long intervals (Ewing and Wolf, Case XI); or (2) the cases were of comparatively mild type and recovered under treatment without abortion (Underhill and Rand, Cases II and IV, and Whitridge Williams's 'neurotic' cases); or (3) were of yet another type in which the index remains low or even subnormal though the clinical symptoms are severe (Whitridge Williams, second series, Case III; Ewing and Wolf, Cases X and XII; Stone, Cases I and II); further investigation of cases of this nature is very desirable. It seems clear that the affections of pregnancy accompanied by vomiting are not all of the same nature, and no one of the classifications proposed has proved satisfactory. In view of the complexity of the factors which regulate the output of ammonia (see above) it is not surprising that this quantity shows no constant behaviour in this collection of disorders; the table draws attention to a feature which occurs in a certain proportion of cases.



TABLE VII.

*Underhill and Rand, Case I.*

	Ammonia Index.
Feb. 16	5.2
" 17	7.8
" 19	7.0
" 20	6.6
" 22	6.3
" 23	23.0
" 24	26.6
" 26	38.7
" 27	41.0

Underhill and Rand state that 'the sudden large increase in ammonia nitrogen on February 23 is to be explained as the result of the practically complete disappearance of glycogen'. In the absence of any data, such as are readily obtained on animals, showing the duration of fasting necessary to remove the store of glycogen in man, one can only say that this may or may not be the correct explanation. One may note that the patient in question had been in a state of practically complete starvation since February 8, i. e. for fifteen days only, and that Benedict's subject showed no such change in thirty-one days, though one is not of course able to compare the initial states of nutrition in the two cases.

Possibly the abrupt rise in the ammonia index is the result of a sudden increase in the formation of acetone bodies, such as is known to occur in another condition of acidosis with vomiting, namely, the cyclical vomiting of children. Speaking of the amounts of acetone bodies excreted in that disorder, Marriott (25) says: 'We have determined a large amount in urine voided at seven in the morning, when the initial vomiting had been at two that same morning. Such quantities cannot be accounted for on the basis of starvation.' No conclusion can be reached on this point while we have no complete data upon the formation of acetone bodies in even a single case of pernicious vomiting (see under (4) below).

In comparing the effects of simple starvation and of persistent vomiting one must bear in mind the important difference, that in the latter condition there is a deprivation of water as well as of food. This will, of course, hinder the removal of acid from the blood by the kidneys, whether in the form of acid phosphates or of substances such as aceto-acetic and  $\beta$ -oxybutyric acids, as Marriott (25) has pointed out in dealing with the importance of shortage of water in the acidosis which accompanies infantile diarrhoea. Possibly this factor may account for some of the differences between the effects of simple starvation and of vomiting.

3. In this type of case, in which the ammonia index reaches a high figure (30 to 50), the effect of abortion is to produce an immediate and rapid fall in the amount.

TABLE VIII.

*Fall of Ammonia Index after Abortion.*

Present paper	Case I	31.1 to 15.6 in 2 days
	Case II	46.2 to 16.7 in 1 day
Underhill and Rand	Case I	56.5 to 10.6 in 7 days
Ewing and Wolf	Case XI	40 to 15.9 in 5 days
Whitridge Williams, 1st series	Case I	32 to 12 in 2 days
	Case II	39 to 18 in 2 days
Whitridge Williams, 2nd series	Case I	29 to 13 in 4 days
	Case II	36 to 11 in 3 days

In Whitridge Williams's first series, Case II showed a transient return of vomiting after abortion, with rise of the index from 18 to 26, and fall to 12 on recovery; in Case III the index, which had reached 21 only before abortion, rose to 48 before death, which took place two days after the operation.

4. It may be well to draw attention to the extreme scarcity of data on the part played by the acetone bodies in the pathology of the affections included under the name of pernicious vomiting. Whitridge Williams (15, 24) makes no mention of them in his descriptions of ten cases, though elsewhere in one of the two papers (24) he says that 'acetone, diacetic, oxybutyric acid, and allied substances were not found in the urine'; no assistance is given to those who may wish to know what these 'allied substances' would be. Underhill and Rand (3) demonstrated the presence of the three acetone bodies in the urine of their Case I, but no quantitative data are given; apparently in the other three cases the matter was not investigated. Ewing and Wolf (11) record that acetone and aceto-acetic acid were present in one, and absent in two, of their six cases; they conclude that their absence is 'of little significance and their quantities entirely out of proportion to the severity of the symptoms'. Without more detail this is not very convincing; it may apply to the cases in question, but it is difficult to believe that the amounts of abnormal acid produced by our Cases I and II were not of considerable importance. Losee and van Slyke (5) make no mention of the acetone bodies. The only estimations of both aceto-acetic and  $\beta$ -oxybutyric acid in a case of pernicious vomiting which we have found in the literature are those made on two days in one case by Sellards (17); the amounts found were small, but the observations were made a week after the performance of 'hysterotomy' at the third month of pregnancy, and the clinical course of the case is not clearly described. The results in this case are described further below ((5), p. 74).

The aceto-acetic acid was determined in our Case II, and these appear to be the only estimations of acetone bodies which have been made in the most acute stage of the disorder; unfortunately it was on most days impossible to secure complete collection of the urine. The output reached 5.57 grm. on the day before the abortion; on the analogy of other conditions of acidosis it is very probable that the amount of  $\beta$ -oxybutyric acid was three or four times greater than that of the aceto-acetic acid (Neubauer (26) and Kennaway (8)); the total output of

acetone bodies would then have been as large as is found in many cases of severe diabetes. The highest amounts of acetone bodies which we have found recorded in the literature as the result of simple starvation are those in the altogether exceptional case (Mrs. M.) of Folin and Denis (22), and in the fasting woman observed by Bönniger and Mohr (21). These are given in the table below; the results of an experiment upon himself by Dr. George Graham (Kennaway (8)) are included for the purpose of comparison, as they show the more usual effect of a short fast.

TABLE IX.

	Grm. per Day.			
	Acetone + Aceto-acetic Acid as Aceto-acetic Acid.	$\beta$ -oxybutyric Acid.	Ammonia Nitrogen.	Ammonia Index.
<i>Fasting</i>				
Bönniger and Mohr, 14th day	3.94	17.6	1.24	30.6
Folin and Denis (Mrs. M.) 4th day	4.01	18.5	2.5	26.6
Dr. Graham 3rd day	0.92	1.59		
<i>Pernicious Vomiting</i>				
Case II	5.57	?	2.71	44.3

5. To illustrate further the inadequacy of our knowledge of those disorders, one may note that there is not yet agreement as to even the direction in which the acid-base equilibrium of the body is affected in them. A high ammonia index, when beyond the limit which can be accounted for by the diet, is usually taken to indicate an acidosis, i.e. the production of abnormal amounts of acid in the body. However, observations such as the following must be taken into account:

(a) Sellards (17) records a case of pernicious vomiting in which (1) the ammonia index was high (32); (2) the output of abnormal acids not large (the percentage of aceto-acetic acid stated would have produced a faint ferric chloride reaction); and (3) the tolerance to sodium bicarbonate (i.e. the amount required to render the urine alkaline) was normal. Unfortunately, as is usual in these cases, the total day's output of nitrogen, ammonia, and acetone bodies could not be ascertained. He contrasts with this case one of diabetes, in which (1) the ammonia index was not raised (6.4); (2) the amount of acetone bodies not greater than in normal urine; and (3) the tolerance to sodium bicarbonate distinctly raised. He suggests that in the latter case an unknown acid was being produced, and that in the former there was a 'primary disturbance of protein metabolism' with formation of abnormal amounts of ammonia; if this be the case, the condition is of course one of alkalosis and not of acidosis. Some comment upon this explanation may be given below after considering the results of Losee and van Slyke, but one may note in passing that it is rather difficult to imagine the nature of this primary disturbance of protein metabolism,

and one would wish to know whether such change occurred under any other conditions. For an actual instance of an alkalosis<sup>7</sup> one may refer to the condition following upon parathyroidectomy in dogs (Wilson, Stearns, and Thurlow (27)).<sup>8</sup> Nothing is easier than to speculate upon the part played in any disease by one or more ductless glands, and it has of course been suggested that the high ammonia output in pernicious vomiting is due to defective action of the parathyroids (Ewing (2)), but no useful purpose is served thereby until fuller investigation of the blood, expired air, and urine has been made.

If the explanation put forward by Sellards is to be accepted, one would have to consider the possibility that the aceto-acetic and  $\beta$ -oxybutyric acids excreted in such cases are produced to neutralize the excess of ammonia, just as in an acidosis, such as that of severe diabetes, ammonia is diverted to the neutralization of these same acids. The high acidity of the urine in cases such as our Case I on June 16 and 17 shows that such neutralization must be more than sufficiently carried out; in fact, this observation is by itself sufficient to cast considerable doubt upon the view advanced by Sellards.

(b) Losee and van Slyke (5) determined the ammonia index and the CO<sub>2</sub> carrying power of the plasma in a series of cases of normal and abnormal pregnancy. Unfortunately no information is given as to the production of acetone bodies. Table X is compiled from their results.

TABLE X.  
*Losee and van Slyke.*

	Ammonia Nitrogen. % of Total Nitrogen.	c.c. of CO <sub>2</sub> bound by 100 c.c. of Plasma.	Average.
Normal	(3.0 to 5.0, Folin)	55 to 75	65
Healthy pregnancy 13 cases	4.4 to 6.7	49 to 63	55.6
Pernicious vomiting			
Case I	31.2	62	
Case II	17.5	52	
Case III	29.0	41	

Losee and van Slyke remark: 'It is noteworthy that although the cases of pernicious vomiting show strikingly high ammonia figures, the plasma bicarbonate indicates no greater degree of acidosis than may be observed in non-toxic pregnancy.'

It is obvious that the question underlying the interpretation of the results of Sellards and of Losee and van Slyke is, What is the most reliable indication

<sup>7</sup> Hasselbalch (16) promises to bring forward evidence that in some cases of acidosis due to acetone bodies an over-compensation by diversion of ammonia occurs, so that the condition is converted into one of alkalosis. One is reminded of the experiments of Barcroft, Graham, and Higgins (29) upon the effect of carbohydrate-free diet upon the dissociation curve of haemoglobin; in some cases the curve was shifted in the manner associated with addition of alkali.

<sup>8</sup> Feeding with thyroid substance produces an acidosis in rabbits (Kuriyama (28)); possibly the preparation contained parathyroid as well.

of acidosis? In both cases the writers seem to assume that the amount of alkali reserve of the blood is of more value for this purpose than is the ammonia index. However, the importance of the ammonia index has been emphasized by Münzer (30) and by Hasselbalch (16). Münzer and his fellow workers investigated the evidences of acidosis shown by healthy men to whom hydrochloric acid was administered. Their results may be summarized as follows:

TABLE XI.  
*Begun, Hermann, and Münzer.*

	CO <sub>2</sub> Tension of Venous Blood (Plesch Method) % of Atmosphere.	Averages for each Period.		
		Acidity of Urine c.c. 0.1 N per day.	Ammonia. grm. per day.	Ammonia Nitrogen. % of Total Nitrogen.
Subject H				
Preliminary period (6 days)	6.08	459	0.76	4.50
HCl taken (9 days)	5.99	665	1.45	7.89
Subject B				
Preliminary period (3 days)	6.00	404	0.92	5.65
HCl taken (3 days)	5.98	567	1.59	9.58

Both subjects showed during the period of administration of acid a very distinct rise in the absolute and relative amounts of ammonia, but no significant fall in the CO<sub>2</sub> carrying power of the blood; the condition was therefore of the same type as that observed in pernicious vomiting by Sellards, and by Losee and van Slyke, and throws considerable light upon their observations, since in Münzer's subjects an acidosis, in the sense of the introduction into the body of an abnormal amount of acid, is known to have occurred. It is clear from the results given in the table above that this acidosis was dealt with chiefly by the utilization of ammonia, and that the chief CO<sub>2</sub> carrying base of the blood, namely sodium, was not diminished. This is after all only what one might expect; the ammonia will otherwise have to be converted into the neutral substance urea to avert its own toxic action, whereas the sodium of the blood is indispensable for the transport of CO<sub>2</sub>. Nevertheless, it is of course difficult to see how it is brought about in the body that an acid is excreted in combination with one base in preference to another, when both these are present in the body fluids. Münzer concludes that the alkali reserve of the blood becomes diminished only in severe and long-continued states of acidosis, such as are seen in diabetics. Similarly Hasselbalch (16), as the result of a minute investigation of the relations between the H-ion concentration of the urine and the ammonia index, comes to the conclusion, best given in his own words, that 'die erste Schranke gegen eine drohende Demineralisation bei übermässiger Säureanhäufung von der auf das feinste regulierten Ammoniakproduktion gesetzt wird. Erst wenn diese Schranke gebrochen ist, wird die Natriumreserve des Blutes in Angriff genommen . . .' But one must note that this first line of defence appears to be broken even by the slight acidosis of normal pregnancy (see under (1)



above), since the slightly raised ammonia index is accompanied by a diminished alveolar  $\text{CO}_2$  tension which Hasselbalch in the same paper speaks of as 'einer sukzessiven Na-Verarmung des Blutes entsprechend'. There is clearly great need for the comparative study by the same methods of all the different conditions in which acidosis occurs, or is thought to occur; we have not found in the literature a single estimation of the alveolar  $\text{CO}_2$  in pernicious vomiting. Unfortunately Hasselbalch's published observations do not as yet include results obtained by the same methods in the most definitely pathological conditions such as pernicious vomiting.

In these considerations may lie the explanation of the apparently anomalous results obtained by Sellards and by Losee and van Slyke. One must bear in mind that pernicious vomiting is a disorder of comparatively brief duration; when a severe stage is reached the condition must terminate in death or improvement in at most two months, whereas some diabetics will continue for years to dispose of large quantities of abnormal acids. Possibly during the much shorter course of pernicious vomiting the neutralization is maintained chiefly by the diversion of ammonia; this would account for the very high indices met with, and for the negative result of tests for depletion of the alkali reserve of the blood. A similar condition perhaps occurs in some cases of diabetes, as in one described by Poulton (31), in which the ammonia index was distinctly raised (14 per cent.) while the alveolar  $\text{CO}_2$  was practically within normal limits. It is not of course maintained that ammonia is the only base which is drawn upon; the increased output of calcium which has been so often employed as an indication of acidosis (see, for instance, Gerhardt and Schlesinger (32), and Sawyer, Baumann, and Stevens (33)) has been observed also in pernicious vomiting (Halverson, Mohler, and Bergeim (34)); in this case the amount excreted was reduced to 8 per cent. of its previous value by administration of sodium bicarbonate.

It is clear from the results brought together here that but slow progress in the investigation of these disorders is to be expected so long as each case is examined by the very limited number of methods which are within the capacity of isolated workers. There are the most obvious probabilities of fallacy in criticizing the results obtained in one case in the light of those derived by different methods from another. Essential data will always be wanting until individual cases can be investigated by every one of the numerous methods now available for the study of acidosis; this requires an organization of workers not easy to provide.

In conclusion, one may note that, of all the features of pernicious vomiting, the one that has attracted the least attention from investigators is the vomiting. This process has been evolved as a protective mechanism, serving to rid the body of harmful substances; possibly some new method of research could be found in this direction. Although the one and only fact ascertained as to the cause of this affection seems to be that it is associated with pregnancy, its pathology might nevertheless be considered in conjunction with that of the



cyclical vomiting of children, to which it presents some resemblance both in its recurrence in susceptible individuals and in the fact that the vomiting is a preliminary to similar changes in metabolism which seem too great and rapid to be the result of simple defect in nutrition.

#### *Conclusions.*

1. In some forms of pernicious vomiting a stage is reached when the ammonia index shows a rapid increase in the course of a few days to values between 30 and 50; at this time the acetone bodies are being produced in large amounts. The changes observed seem too great and sudden to be the result of starvation alone. When this condition appears, abortion seems to be the only treatment which is of any avail, and rapid improvement is to be expected from it in the great majority of cases.

2. Attention is drawn to the great scarcity in the literature of adequate analyses of the urine in this disease, especially in regard to the output of acetone bodies. Further differentiation of the various forms of pernicious vomiting is required, since in some recorded cases the ammonia index is even subnormal.

3. Such results as have so far been obtained as to the state of the alkali reserve of the blood in pernicious vomiting suggest that ammonia is very efficiently utilized in the preservation of this reserve.

In conclusion, we wish to express our thanks to Mr. Comyns Berkeley for permission to publish the notes of his cases.

#### *Note on Tests for Aceto-acetic Acid.*

1. Most clinical text-books assert that the ferric chloride test is a test for aceto-acetic acid, while Rothera's nitroprusside test (35) is a test for acetone; this form of statement is wholly misleading. The significance and relative delicacy of the two tests may be tabulated as follows:

Test.	Acetone.	Reaction with Aceto-acetic Acid.
Ferric chloride minimum	nil	+ 1 in 8,000
Nitroprusside (Rothera) minimum	+ 1 in 20,000	+ 1 in 400,000

Thus Rothera's test is in no way distinctive of acetone as against aceto-acetic acid, but is even twenty times more sensitive to the latter substance than to the former.

2. If Rothera's test were given, as is usually stated, by acetone alone, there would be no object in performing it. Arnold (36) showed in 1900 that quite fresh urine contains no or very little acetone, however much aceto-acetic acid

be present; the amount of acetone produced subsequently by decomposition of the aceto-acetic acid in the urine throws no light upon the condition of the patient. The separate detection of these two substances, which is generally required of a clinical laboratory, is therefore futile.

3. The following terms may be found useful in recording from day to day the strength of the Rothera reaction: (a) 'quick-strong', a deep permanganate colour appears within a minute of mixing; (b) 'slow-strong', the same colour takes several minutes to develop; (c) 'quick-weak', a conspicuous pink colour is produced in a few minutes; (d) 'slow-weak', the smallest amounts (up to 1 in 400,000) are detected by looking for a pink zone above the ammonium sulphate crystals; this may take half an hour to develop.

4. The great difference in delicacy of the two tests (see table) is of service in judging of the amount of aceto-acetic acid present. The ferric chloride reaction is not obvious with less than 1 in 1,400 of the acid, though with care 1 in 8,000 can be detected. Urines giving Rothera reactions within the range of 'slow-strong' may or may not give the ferric chloride test (see Case I, June 22 and 28); it is obvious that any one who in the light of current statements relied upon ferric chloride alone for the detection of the acid might miss amounts of it which are of considerable importance in watching the state of a patient from day to day. Both tests should always be performed unless the ferric chloride reaction is so strong, or the Rothera so weak, that the other is unnecessary.

The greater part of this note is derived from a paper by Hurlley (37), in which a full account of these and other tests is given.

#### REFERENCES.

1. Ewing, *Arch. Int. Med.*, Chicago, 1908, ii. 485.
2. Ewing, *Amer. Journ. Med. Sci.*, Phila., 1910, cxxxix. 828.
3. Underhill and Rand, *Arch. Int. Med.*, Chicago, 1910, v. 61.
4. Leathes, *Proc. Roy. Soc. Med. (Pathology)*, Lond., 1907-8, 131.
5. Losee and van Slyke, *Amer. Journ. Med. Sci.*, 1917, cliii. 94.
6. Frew, *Proc. Roy. Soc. Med. (Anaesthetics)*, Lond., 1911-12, 60.
7. Folin, *Amer. Journ. Physiol.*, 1905, xiii. 45.
8. Kennaway, *Biochem. Journ.*, Camb., 1914, viii. 355.
9. Sellards, *Johns Hopkins Hosp. Bull.*, Baltimore, 1914, xxv. 141.
10. Janney, *Zeit. f. physiol. Chem.*, Strassburg, 1911-12, lxxvi. 99.
11. Ewing and Wolf, *Amer. Journ. Obstet.*, N. York, 1907, lv. 289.
12. Stone, *Med. Record*, N. York, 1905, lxviii. 295.
13. Satta, *Hofmeister's Beitr. z. Chem., Physiol. u. Pathol.*, Braunsch., 1905, vi. 22.
14. Hasselbalch and Gammeltoft, *Biochem. Zeits.*, Berlin, 1915, lxviii. 206.
15. Whitridge Williams, *Johns Hopkins Hosp. Bull.*, Baltimore, 1906, xvii. 71.
16. Hasselbalch, *Biochem. Zeits.*, Berlin, 1916, lxxiv. 18.
17. Sellards, *Johns Hopkins Hosp. Bull.*, Baltimore, 1912, xxiii. 289.
18. Benedict, *A Study of Prolonged Fasting*, Washington, 1915.
19. Cathcart, *Journ. Physiol.*, Camb., 1906-7, xxxv. 500.
20. Brugsch, *Zeit. f. exper. Path. u. Therap.*, Berlin, 1905, i. 419.
21. Bönniger and Mohr, *ibid.*, 1906, iii. 675.

22. Folin and Denis, *Journ. Biol. Chem.*, Baltimore, 1915, xxi. 183.
23. Nebelthau, *Zentralblatt f. inn. Med.*, Leipz., 1897, xviii. 977.
24. Whitridge Williams, *Amer. Journ. Med. Sci.*, 1906, cxxxii. 343.
25. Howland and Marriott, *Johns Hopkins Hosp. Bull.*, Baltimore, 1916, xxvii. 63.
26. Neubauer, *Verhand. deutsch. Kongr. inn. Med.*, Wiesb., 1910, xxvii. 566.
27. Wilson, Stearns, and Thurlow, *Journ. Biol. Chem.*, Baltimore, 1915, xxiii. 89 and 123.
28. Kuriyama, *Journ. Biol. Chem.*, Baltimore, 1918, xxxiii. 215.
29. Barcroft, Graham, and Higgins, *Journ. Physiol. Proc.*, Camb., 1912-13, xlv. 47.
30. Begun, Herrmann, and Münzer, *Biochem. Zeits.*, Berlin, 1915, lxxi. 255.
31. Poulton, *Guy's Hospital Gazette*, Lond., 1915, xxix. 394.
32. Gerhardt and Schlesinger, *Archiv f. exper. Path. u. Pharm.*, Leipz., 1899, xlii. 83.
33. Sawyer, Baumann, and Stevens, *Journ. Biol. Chem.*, Baltimore, 1918, xxxiii. 103.
34. Halverson, Mohler, and Bergeim, *ibid.*, 1917, xxxii. 171.
35. Rothera, *Journ. Physiol.*, Camb., 1908, xxxvii. 491.
36. Arnold, *Zentralblatt f. inn. Med.*, Leipz., 1900, xxi. 417.
37. Hurtley, *Lancet*, Lond., 1913, i. 1160.

## AN OBSERVATION UPON METHAEMOGLOBINAEMIA OR SULPH-HAEMOGLOBINAEMIA

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DURING the past sixteen years since the publication of the report by Professor Stokvis of the first case of a patient suffering from a condition similar to the one herein recorded, a number of later cases diagnosed as either methaemoglobinaemia or sulph-haemoglobinaemia have been placed on record. Garrod in Allbutt and Rolleston's *System of Medicine* discusses the condition under enterogenous cyanosis and gives references to the formerly reported cases up to and including that of Wynter and Essex (1908). Since then additional cases have been reported by Wood Clarke and Curtis (1), Haldin Davis (2), Mackenzie Wallis (3), and more recently one by W. C. Lang and E. I. Spriggs (4).

*Case report.* An unmarried man (a soldier) 22 years of age was admitted to the Hampstead Military Hospital on June 13, 1917. At the time of admission he had no complaints, and said he felt quite fit. His family history was negative.

In civil life he had been employed as a clerk. The patient stated that before enlisting in the Army he had been in good health and had played football, cricket, and other games without difficulty. Apart from the statement that a tonsillectomy was performed when he was nine years of age, there was no history of any previous illness or infection. He had smoked cigarettes in moderation but had always been a teetotaler.

In May 1913 he enlisted with the regular army and performed the required training and duties without experiencing any difficulty. In October 1914 he was sent with an infantry battalion to France and went immediately to the firing line. Here he carried on and enjoyed good health until May 1915, when he received a shrapnel wound in the left arm and hand. Following this he was off duty for two months, but in July 1915 rejoined his unit and returned to the line. He was at this time quite fit, and continued doing full duty for the subsequent seventeen months without the appearance of any abnormal symptoms. He stated that since the beginning of the year 1917 he had suffered from headaches which had been progressively increasing in frequency and intensity. From February 1917 until the time of admission into the Hampstead Hospital he had had four attacks of a peculiar and especially severe character, during which he suffered from dizziness, palpitation, shortness of breath, and precordial pain. The onset of these attacks was usually preceded by a period of several days during which the patient suffered from intense headache. The actual attacks had each been of several hours' duration. No exciting cause was demonstrable. After each of these attacks the patient would feel quite fit, and much better in fact than for several days prior to their appearance. He ascribed

his improvement at this time chiefly to the disappearance of the headache, there usually being no recurrence of this symptom for a period of several days.

*Physical examination.* The patient was bright and intelligent and complained of no subjective symptoms. He was well nourished and of normal muscular development. There was a slight pallor of the lips suggesting the presence of a moderate degree of anaemia. His hands were warm, dry, and not cyanosed. The thyroid was not enlarged nor were enlarged glands palpable. The tonsils were slightly enlarged, the right one more so than the left. His teeth were excellent, and the gums in good condition. Examination of the lungs revealed nothing abnormal. The abdomen was normal in appearance. The liver and spleen were not palpable. The knee-jerks were active and equal.

*Heart.* On inspection a fairly forceful, localized impulse was visible in the fifth intercostal space, situated 8.5 cm. to the left of the mid-sternal line, being well inside the nipple line. On percussion the left border of cardiac dullness in the fifth intercostal space was 11 cm. from the mid-sternal line, and the right border in the fourth intercostal space was 3.5 cm. beyond the mid-sternal line. On auscultation the heart action was regular and the rate not increased. The sounds were of good quality and no abnormal accentuations were heard. At the apex and also at the second intercostal space, on the left side, close to the sternal margin, a faint systolic murmur was audible. The radial pulses were equal, of good quality, and the arterial walls not thickened.

The patient's reaction to a stair-climbing test—going rapidly once up and down two flights, each of twenty stairs—was good. His pulse-rate before the exercise was 72, immediately afterwards it had increased to 116, and at the end of two minutes' rest was 76 per minute.

For two weeks following his admission to the hospital the patient was up and about, and was treated as a mild case of 'irritable heart'. He was placed on daily fifteen-minute physical exercises, which he undertook without difficulty, and with a normal response. On June 26 he had to 'fall out' from the exercise on account of dizziness. This dizziness actually appeared before the commencement of the exercise. When seen a few minutes later his pulse-rate was 82 and the only objective sign was a very noticeable pallor. He was ordered to bed, and when seen several hours later he had regained his normal appearance. The following day he was up and about as usual, but was excused from the physical drill. At this time the patient complained frequently of severe frontal headaches, and several powders containing 5 gr. each of aspirin and phenacetin were given, but as these were not found to relieve the headache they were discontinued.

On the morning of July 3, on being called to the ward to see the patient, he was found to be in an unusual condition. His colour was that of the moribund. There was a profound cyanosis, and this combined with an intense pallor gave a peculiar leaden aspect to the skin of his face and the rest of his body. The patient was, however, quite conscious. He was lying flat in bed and in no distress. On being questioned he complained of frontal headache and of palpitation. The cyanosis and pallor of the features were general but were most intense in the lips and ears. The tongue was coated, and with the buccal mucous membranes was of a deep purple colour. The hands were deeply cyanosed, but showed the presence of a fairly active capillary circulation. The finger-tips were cold, the remaining portions of the hands were warm. The cyanosis extended to the forearms. The feet were cyanotic, the toes being cold and the circulation slow. The patient's temperature by mouth was 98°. The respirations were 20 to the minute, quite regular and normal in depth. The veins were not distended. The heart rate was 140. On palpation the radial pulse was slapping and poorly sustained. An occasional extra-systole was noted, otherwise the pulse was quite regular. Pulsation could be readily seen in the temporal arteries well above the zygoma, and at this point the pulse was easily palpable and felt tense. The dorsalis pedis pulse on either side was just palpable. The systolic

blood-pressure at this time, taken by the auscultatory method, was on the three successive readings 178, 170, and 168 mm. Hg. The venous and capillary pressures were normal, registering 20 cm. of  $H_2O$  and 36 cm. of  $H_2O$  respectively. The liver dullness was not increased, and the spleen could not be felt. There was an extensive epigastric pulsation. Examination of the heart showed the impulse to be diffuse, its point of maximum intensity being in the fifth intercostal space internal to the nipple line and 8.5 cm. to the left of the mid-sternal line. The left border of cardiac dullness in the fifth intercostal space measured 13 cm. from the mid-sternal line, and the right border in the fourth interspace 3.5 cm. from the mid-sternal line. At the base of the heart, at the level of the second intercostal space, the total width of cardiac dullness was 10 cm. Comparing the measurements of the heart before and during the attack we might conclude that there was perhaps a slight, but at the most no more than a slight, increase in the size of the heart during the attack; such increase as was present took place at all levels on the left side of the mid-line, the right border in both instances being alike. On auscultation, at the apex the first sound was accentuated and unaccompanied by any murmur. At the second left costal cartilage a harsh rasping systolic murmur could be heard; this was not accompanied by a thrill, and the murmur faded away rapidly in every direction.

Amyl nitrite, one pearl, was administered by inhalation for the purpose of noting the physiological effect, and also expecting that the vaso-dilatory action of the drug might diminish the symptoms. The drug was given at a time when the real nature of the malady was unsuspected, though it was recognized that the case was quite unusual, and that the cyanosis was not of cardiac origin. The effect of the amyl nitrite, however, was the reverse of what had been expected. Following the inhalation the pallor and cyanosis both increased; also the patient complained of a 'bursting sensation' in the head and chest. The pulse-rate one minute before the drug was given had been 132 to the minute, one minute after the inhalation commenced the rate increased to 204. A few minutes later the rate fell to 140. Blood-pressure readings made by auscultation just prior to the giving of the amyl nitrite showed the systolic pressure to be 154 mm. Hg; one minute after the administration this increased to 180 mm. Hg.

The patient's condition, as it has been described, continued for a period of some hours. During the afternoon of that day he slept, and when he awakened about the middle of the afternoon the headache and palpitation had disappeared and he felt quite well. He was still pale and cyanotic, but remarkably less so than during the height of the attack. The following morning he had no complaints, but it was noted that he was paler than usual and that a slight but definite degree of cyanosis persisted. The heart-rate was normal, and the character of the sounds quite altered from what they had been on the previous day. The systolic murmur, heard loudly at the base during the attack, was now barely audible. Blood-pressure readings showed the systolic pressure to be 128 and the diastolic 70 mm. Hg.

Examination on the second day following the attack showed the patient to be quite comfortable. The pulse-rate was 80 and the respirations 18 to the minute. There was no pallor apart from the anaemia. The mucous membranes were pale, but no cyanosis was evident in the tongue or lips. The hands were cold and moist and showed the presence of some cyanosis. The feet were cold and very slightly cyanosed. In both the hands and feet the capillary circulation was slow. The pulse was regular, rather small, but well sustained. Pulsation was visible in the temporal arteries in front of the ears and just above the zygoma. The pulsation in the dorsalis pedis arteries was just perceptible in either foot. The systolic blood-pressure by auscultation was 132, 132, and 133 mm. Hg. on three successive readings. No venous engorgement was visible. On July 4 the venous pressure was 16 cm. of  $H_2O$  and the capillary pressure



34 cm. of  $H_2O$ , and on July 5 the corresponding pressure readings were 17 and 30 cm. of  $H_2O$ .

The abdomen was relaxed and there was no distension. The epigastric pulsation was still quite noticeable, but was not nearly so pronounced as during the attack. The liver dullness was not increased and the spleen could not be felt.

Examination of the heart showed the size to be practically as it had been before the attack. On auscultation with the patient in the horizontal position, the first sound at the apex was followed by a faint systolic murmur. The second sound in this area was normal. At the second left costal cartilage the systolic murmur had entirely disappeared. The second sound in this area was accentuated. With the patient standing upright, the first sound at the apex was reduplicated and accentuated. At the base over both aortic and pulmonary areas the sounds were clear and unaccompanied by murmurs.

On being questioned regarding the onset of the attack and the nature of the subjective symptoms, the patient gave the following description: On the evening prior to the attack he felt quite as well as usual, but on the following morning awakened about six o'clock with a severe frontal headache. He got up, however, and at 7.30 o'clock went to the patients' dining hall for breakfast. He did not feel inclined to eat anything and for breakfast had only a cup of tea. Returning to the ward he had one flight of stairs to ascend. On coming up these stairs he noticed that he was very short of breath and had palpitation. On reaching the ward he complained of an uncomfortable feeling of tightness across the chest and was unable to get a satisfying breath. At this time the patients in the ward remarked on the 'green' colour of his face. He lay down for about one hour, then feeling somewhat better got up, and without reporting to the sister in charge of the ward proceeded to do some light duties about the hospital. With the exception of the persisting severe headache he felt fairly well, though he thought that probably his appearance had not improved. After working for about fifteen minutes the symptoms which he had experienced when coming up the stairs earlier in the morning returned, together with a throbbing sensation in the head and a peculiar 'feeling of fullness' in the fingers and toes. This 'feeling of fullness', he said, gave the extremities the sensation of being placed on a vibrator, and when walking he felt as though he were placing his feet on a very thick carpet. The patient returned to his bed at this time, and a few minutes later the examination recorded above was made.

A blood examination during this first attack showed:

Haemoglobin (Haldane)	. . . . .	76 per cent.
R.B.C.	. . . . .	5,500,000 per cm.
W.B.C.	. . . . .	6,600 " "
Differential:		
Polymorphonuclears	. . . . .	46 per cent.
Lymphocytes (large)	. . . . .	14 " "
" (small)	. . . . .	28 " "
Oxyphils, coarse granular	. . . . .	6 " "
Mononuclears	. . . . .	5 " "
Unclassified	. . . . .	1 " "

No change was observed in the appearance of the red blood cells.

A urine analysis was made at the same time:

Colour—light amber, clear.

Sp. g.—1027.

Reaction—alkaline to litmus.

" acid to phenolphthalein.

Albumin—nil. Blood—nil (chemical).

Sugar—nil. Bile salts—nil.

During the time the patient remained in the Hampstead Hospital, which extended over a period of five months, he had four severe and several mild attacks, all similar to the one described. All these were of about equal duration, coming abruptly and vanishing quickly and continuing for a few hours only. Between the attacks the patient was continually up and about, and, with the exception of rather frequent headaches, he had no complaints, and presented no abnormal physical signs.

During an attack which occurred on July 16, which was in all respects similar to the one already described, about 20 c.c. of blood were drawn from a vein in the patient's arm. The blood was exceptionally dark in colour, being almost of a chocolate-brown hue. This brownness persisted on dilution of the blood with water and on shaking with air. A report on the appearance, gross and microscopic, also on the spectroscopic findings of this blood, is given below. Specimens of urine obtained during the attack and also twelve hours and more later were clear, and of the usual pale amber hue. Diluted specimens of blood, taken on several successive days following the attack, were of precisely the same tint as diluted specimens of control blood. An electro-cardiogram was made during the height of the attack and showed no abnormal features; it was in all the essential features similar to a control electro-cardiogram made while the patient was in his normal condition. The duration of this second attack was five hours.

On August 18 the patient had a third attack which continued for a period of about ten hours. It was on the day following this attack that the patient's liver and spleen were for the first time made out to be enlarged. The liver edge could be felt 2 cm. below the right costal margin in the mammary line, and on percussion flatness extended as high as the fifth interspace. The spleen could be distinctly felt on deep inspiration 2 cm. below the costal margin, and was fairly firm in consistency. One week later the liver had returned to the costal margin, and at this time flatness extended up as high as the sixth interspace. The spleen progressively decreased in size, and at the end of two weeks was no longer palpable.

On September 22 the patient had another attack similar in character and of about the same duration as those preceding. From this time until his discharge from hospital at the end of November there were no recurrences. A culture from the patient's blood taken on November 22 was sterile.

A blood examination was also made on November 22, and showed the following:

Haemoglobin	. . . . .	85 per cent.
R.B.C.	. . . . .	5,040,000 per cm.
W.B.C.	. . . . .	8,200 " "

Differential:

Polymorphonuclear	. . . . .	70 per cent.
Lymphocytes (large)	. . . . .	12 " "
" (small)	. . . . .	17 " "
Eosinophils	. . . . .	1 " "

The red cells were normal in appearance. There appeared to be a slight excess in the number of blood platelets.

The patient was not confined to bed at any time, and was allowed passes to leave the hospital during the afternoons. He had very few complaints, and those he made were usually of headaches. In fact he apparently enjoyed fairly good health. The pallor, however, persisted and had definitely increased during his residence in hospital. He also developed a slight degree of cyanosis, which appeared eventually to be permanent. At no period did he have any obvious

intestinal disturbance. The action of the bowels was quite regular, and the appearance of the stools normal.

We are indebted to Dr. Buckmaster of University College, London, for spectroscopic examination of the patient's blood, and his report is here given :

1. Under the microscope the blood corpuscles are well preserved, non-crenated, and not swollen. They appear to be intact and the liquid is not haemolysed. Compared with the normal blood strata of approximately equal thickness the sheet of corpuscles has a different tint and appears slightly shaded. It has a more pronounced greenish-yellow tint.
2. In capillary tubes of varying bore 0.5, 1, 2 mm. in diameter, the blood by reflected light is brick-dust red, and this is strikingly so when compared with a normal control. This colour does not appreciably vary when the specimen is shaken with air.
3. The reaction of the blood is alkaline to litmus, and more markedly so than is the blood of a normal control.
4. The spectrum is a mixture of oxyhaemoglobin together with a quantity of methaemoglobin or sulph-haemoglobin. The red band is distinct and easily seen when the middle two oxyhaemoglobin bands are seen separated. This red band lies at  $\lambda$  630 and is seen in a stratum 1 cm. in thickness when 0.2 c.c. of blood is diluted to 5 c.c. or in a dilution of 1:25 of water. The appearance would suggest that the haemoglobin is changed in part within the corpuscles.

The deciding tests of the effect on the spectrum of the addition of ammonium sulphide and of acid-free CO were not employed. Judging from the reports of former spectroscopic examinations made on the blood of patients suffering from a similar condition, the position of the red band in the present instance would suggest that we were dealing with a case of sulph-haemoglobinaemia.

In a letter received from the patient almost four months after his discharge from hospital, he states that during this period he has had three attacks similar to those described in the present report. The first two of these he describes as quite mild and lasting each for about five hours. The third was apparently very severe and continued for twenty-five hours. He states that 'during this time there were long bouts of severe palpitation which were rather alarming'. Further, he writes that on the termination of this attack he 'was quite giddy and weak for several days and unusually pale'. For the succeeding three weeks since that attack up to the time of writing he felt fairly well, but suffered continuously from a severe headache and a 'tendency to palpitation on the slightest provocation'. He also complained of nervousness, the slightest noise causing him to 'jump'.

In view of the former cases of this condition which have been reported, the present one appears to be of special interest.

1. In the character of the recurrent attacks, which have all been of short duration, and the comparatively long intervals between the attacks, during which time the patient was practically free from subjective symptoms.

2. The present case also seems to illustrate that within a few hours some unknown agent may reduce a large percentage of the haemoglobin to methaemoglobin (or an ally), and this agent must, to explain the symptoms in our patient, be supposed to introduce itself into the blood stream in considerable amount and rapidly. The quick and apparently complete recovery points to the introduction being brought speedily to an end. Throughout the attacks and during the

periods immediately succeeding them the colour of the urine remained unchanged. The fate of the altered blood pigment does not appear. That the haemopoetic functions became disturbed is indicated by the temporary enlargement of the spleen after the attack of August 18; yet after the attack of July 3 the red cells were not reduced below normal in numbers, and showed no unusual appearance.

The question of addiction to the use of any drug which might be responsible for the symptoms displayed was carefully inquired into and proved entirely negative.

## REFERENCES.

1. Wood Clarke and Curtis, *Medical Record*, New York, 1910, lxxviii. 987.
2. Haldin Davis, *Lancet*, London, 1912, ii. 1145.
3. Mackenzie Wallis, *Quart. Journ. Med.*, Oxford, 1913-14, vii. 73.
4. Lang, W. C., and Spriggs, E. I., *ibid.*, 1918, ii. 102.

## ACUTE INFECTIVE POLYNEURITIS

By JOHN ROSE BRADFORD, E. F. BASHFORD, AND J. A. WILSON

With Plates 1-9

AMONGST the rarer forms of disease observed in the troops in France and Flanders during the present campaign there is a very definite group of cases presenting a remarkably constant clinical picture of generalized palsy of peculiar character. The features of the malady are so constant and uniform that there is really but little difficulty in the immediate recognition of the disease, although it is often overlooked by those not familiar with its manifestations, and there can be little doubt that many cases therefore escape detection. Further, it is probable that atypical forms, more difficult of diagnosis, also exist, but the present communication deals solely with a series of carefully selected typical cases, presenting what may be regarded as all the leading phenomena of the disease.

Cases similar to, if not identical with, those now described have been recorded by other observers, both in civil practice prior to the war, and also by writers during the present campaign. Thus Osler (1) has described such cases under the term of acute febrile polyneuritis, and Gordon Holmes (2) has recorded the clinical and pathological findings in a series of cases similar to ours, and has discussed the differential diagnosis of the condition and its separation from other forms of neuritis and from certain affections of the nervous system such as poliomyelitis and Landry's paralysis. Gordon Holmes's observations on the clinical features of the disease are essentially in agreement with mine.

Isolated instances of the malady were seen by the writer (J. R. B.) from time to time during the earlier period of the war, but a series of cases was more especially observed during the year 1917, and the very remarkable character and distribution of the palsy seemed such a characteristic feature of the disease, that it was decided to make, if possible, a more complete study of the malady. The palsy, both in its distribution and character, presented marked differences from that seen in the better-known varieties of neuritis, and still greater differences from that seen in poliomyelitis. It was difficult, even when only the clinical phenomena were considered, to look upon the disease as a neuritis or, at any rate, as a neuritis at all similar to the well-recognized varieties of that affection.

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Certain features of the palsy, such as its frequent progressive and occasional ascending character, the marked involvement of the trunk muscles and of the respiratory muscles, suggested a certain resemblance to the well-known palsy seen in some animals, e. g. the rabbit, as a result of the subdural inoculation of the virus of rabies. Hence when material from a fatal human case was available, an attempt was made to see whether the disease could be transmitted experimentally to an animal by a procedure similar to that employed for the experimental transmission of rabies. The experiment proved successful in the monkey, and lesions similar to those found in the fatal human cases were reproduced in the experimental animal. The disease was thus shown to be an infection, and then the question immediately presented itself, of its relation, if any, to poliomyelitis and allied diseases. A series of observations on the isolation and culture of the virus was then proceeded with, and observations on the subdural inoculation of the living culture and the reproduction of the disease experimentally were carried out, with the result that the malady with its characteristic lesions was successfully reproduced in the monkey. Finally, the living virus was recovered from such experimental animal.

This communication is therefore naturally divisible into three parts, for each of which one of us is responsible.

- I. The clinical phenomena of the disease in man. (J. R. B.)
- II. The morbid anatomy of the disease in man and in the monkey, together with the experimental production of the disease in the monkey. (E. F. B.)
- III. The isolation and culture of the virus of the disease. (J. A. W.)

## PART I

### THE CLINICAL PHENOMENA OF THE DISEASE IN MAN

BY JOHN ROSE BRADFORD

This account of the clinical manifestations of the disease is founded on the observation of a series of thirty cases. In twenty cases, notes of the cases were available; in the other ten, for a variety of reasons dependent upon the exigencies present at the time, no full notes were obtained, but no case is included that was not quite typical in its manifestations, and all cases were seen by the writer.

*Onset.* Two modes of onset may be recognized; in one, including the great majority of the cases, there is a definite history of an illness with general symptoms, prior to the onset of the palsy. In the second group, including but a small proportion of the total cases, the patients state that the first manifestation of illness is the actual development of the palsy. It is probable that the first mode of onset should be regarded as the typical one. In the series of twenty cases where full notes are available, there are fifteen cases with a definite history



of an initial illness, and four cases where, according to the patient, the first symptom was either weakness, or weakness together with tingling of the legs. In the remaining case, which is one of considerable importance owing to the fact that the patient, Case III, was acting as an orderly in a hospital at the time of the onset of the palsy, and was therefore under medical observation, a sudden weakness of the legs was apparently the initial symptom, but five to six weeks before he had suffered from very severe headache, and it is very probable that this was really the initial manifestation of the disease.

#### *The Initial Illness.*

Although a history of an initial illness can be elicited in the majority of cases, this illness is usually of a mild type with no very severe symptoms. It is probable that this is the reason why in a certain proportion of the cases no such history is obtained; in other words, the soldier does not attribute any importance to the slight and transitory symptoms that may really have been present. In a small proportion of the cases, the initial symptoms are sufficiently severe, and are of such a character as to suggest the possible existence of cerebro-spinal meningitis; this, however, is quite exceptional. The most constant initial symptoms are moderate fever, headache, vomiting, and pain in the back. Sometimes general limb-pains such as are associated with many febrile states occur; occasionally sore throat may be complained of, and quite exceptionally there may be merely catarrh. In the rare instances when cerebro-spinal meningitis is suspected the headache and vomiting are accompanied by the doubtful presence of some stiffness of the neck. No rash has ever been observed.

Headache is the most constant symptom, and sometimes it is very severe and quite out of proportion to any pyrexia present, as it is most unusual for the temperature to be raised more than two or three degrees. The headache is usually diffuse, but it may be occipital in position, and does not generally last more than two to three days. Vomiting at the onset is also a very constant symptom in association with the headache; it is not usually either severe or repeated, and does not persist.

Pain in the back, down the spine, and in the loins is complained of by many patients, and in some cases is very severe and much aggravated by movement. In a few instances this pain is also felt in the neck, and there is disinclination to move the neck or head, and possibly some slight and doubtful stiffness of the neck. Pain may also be felt in the limbs and in the abdominal wall, but pain of this distribution is more often seen later at the onset of the palsy. The sudden nature of the onset, together with the occurrence of headache, backache, and vomiting, is the cause of the resemblance of severe cases to cerebro-spinal meningitis, but usually there is no great difficulty in the diagnosis, as the patients do not present signs of being gravely ill, and an exploratory lumbar puncture at once shows that meningitis is not present.

Pyrexia is probably always present; it is usually slight, the temperature

rising to 100° F. or 101° F.; in a few cases fever at the onset as high as 103° F. has been observed. The fever is of short duration, lasting two to four days; in one case the patient stated that he had fever for ten days, but no chart was available to check this. All the symptoms subside rapidly in the course of a few days, sometimes only two or three days, and the patient apparently regains his former health, and thus the case is often regarded as one of so-called influenza, trench fever, or pyrexia of uncertain origin. In most cases the illness has been so transitory and mild that the case is discharged from hospital after a very brief stay and rapidly returns to duty, apparently well, and remains so for a variable period prior to the onset of the palsy. In other words, there is a quiescent period, or period of latent infection.

#### *Period of Latency.*

The duration of this interval is difficult to determine with any degree of accuracy, but apparently, if the statements of the patients can be relied on, it is liable to some variation. In Case III, already quoted, the patient during this quiescent period was known to be apparently well, and was doing duty in the ordinary way as a hospital orderly. The initial symptoms in this case were known to have occurred immediately prior to his admission to hospital, and thus in this case the duration of the interval can be determined with some accuracy. Five weeks after convalescence from the initial symptoms and six weeks from the actual onset, this man developed the typical palsy, which was of sudden onset. This case would seem to be of considerable value in determining the length of the quiescent interval, as here it rests on direct observation, and it is notorious that the statements of men as to dates on admission to hospital from the front are not of much value.

An officer gave the following history: Onset of illness sudden, with severe headache and vomiting, together with much aching of the bones and limbs generally. The fever rose to 103° F., and the headache and some fever lasted four to five days. He then returned to duty and felt quite well and was vigorous enough to play football and take part in route marches, until one month from the date of onset, when he suddenly lost power in the legs whilst on a march. He had, however, noticed some numbness in his feet and legs for two days prior to the onset of the palsy. In another case, where the patient was under observation throughout, there was a febrile illness with headache, backache, and pains in the shins. The fever rose to 101° F., and he was kept in hospital ten days and then discharged as convalescent. One week after discharge, and seventeen days from the onset, palsy of the legs, with numbness of the extremities, suddenly occurred.

In other cases the interval would seem to have been still shorter, and this is more especially so in the cases presenting symptoms suggestive of cerebro-spinal meningitis. Thus, in one case the onset was very sudden, with severe headache and vomiting whilst on the march, and three days later definite signs of palsy

were noted, not only in the limbs, but also in the face, together with absence of the knee-jerks. In another case of similar sudden onset with pain in the back, paralytic phenomena were present on the fifth day. It would seem, therefore, that the interval between the initial symptoms and the fully declared palsy may be as long as a month, or even six weeks, and that during this time the patient may be not only apparently quite well, but even able to undergo severe muscular exertion without distress.

In many cases, however, the interval is shorter, and in some no history of any symptoms sufficiently marked to attract the patient's notice is obtained and the first manifestation of the disease is the palsy.

#### *The Fully Declared or Paralytic Stage of the Disease.*

In a few cases, and especially in the less severe forms, the onset of the palsy is noticed only as a general weakness that increases more or less rapidly, and is not obviously more marked in one region of the body than in another, but in the majority of cases, and especially in the more severe ones, the onset of the palsy is more characteristic and dramatic. Thus a common mode of onset is for the patient to lose power suddenly in the legs, so that he falls down when on parade, or even on the march. Sometimes he is unable to rise from the sitting posture, although a short time previously he felt perfectly well, and was unconscious of any trunk or limb weakness. Even when the onset is as sudden and marked as this, the loss of power in the legs does not amount to complete paraplegia, and the patient can often stand, or even walk, with assistance. Further, the extreme weakness present at the onset may diminish to some degree within the next ensuing twenty-four hours, then return and increase in amount still later. Numbness and tingling in the extremities may precede or accompany the onset of the palsy. It is of some interest that at the time of onset of the palsy, pain may also be complained of, especially in the back, and sometimes in the body wall, more especially in the abdominal wall. In a few cases, pain suggestive of a girdle pain has been present. Headache is also common, and is sometimes severe and persistent. Fever is not necessarily present; if it is, it is usually slight in amount, not exceeding 100° F. Occasionally a higher degree of fever is present, e. g. 101° F. or even 102° F. Cases may be seen where the fever is very irregular, the temperature remaining up for one or two days, then falling and remaining normal for several days, and then rising again for a brief period. Bouts of fever of short duration may recur three or four times in the course of as many weeks. It is not always easy to be certain of the cause of the pyrexia, as pulmonary complications are of frequent occurrence, and the pyrexia may in some instances be dependent upon such complications as bronchitis, pleurisy, &c.

In most cases the motor weakness is first complained of in the legs, and is limited at first to the legs. It tends to involve the legs as a whole, and no cases have been seen where it was at first limited to the distal segments of the limb. In some cases, although the patient only complains of weakness of the legs, it is

found on examination that the arms are really also involved; but in many cases there is a distinct interval between the involvement of the legs and that of the arms, and this may be as much as two or even three days. One of the most characteristic features of the palsy of the limbs is the marked degree in which the paralysis involves the proximal segments of the limb. Thus it is common to observe that the movements of the shoulder and of the hip are extremely weak or absent at a time when the patient can still move the fingers or toes freely. A patient unable to raise his leg from the bed may yet move his toes freely, and a man unable to raise his arm may be able to roll a cigarette if the materials are placed in his hands. The palsy never picks out individual muscles in a limb, and although a group of large muscles such as those of the hip may be more affected than other muscles, yet the palsy is never limited even to a group of muscles. It may be described generally as a flaccid palsy, affecting, but to a varying degree in different cases, all the limb muscles, but more especially and to a greater degree the large muscles of the proximal segments of the limbs. It is roughly symmetrical in its distribution, although one limb may be, and often is, more involved than its fellow. Another remarkable feature of the palsy is the great frequency with which the muscles of the trunk are involved, and also the degree of palsy so produced. The muscles of the back, abdomen, chest, and even of the neck are prone to be affected in all the more severe cases. Thus the patients are not only unable to raise themselves or sit up in bed, but in many cases are even unable to turn in bed, and often they cannot raise their heads from the pillow.

The muscles of the anterior abdominal wall are also often involved and the palsy of the rectus abdominis is easily detected. Occasionally only a portion of this muscle, e. g. the lower portion, is involved, or probably it is rather that the lower portion is more affected than the upper.

When the trunk muscles are much involved the patient's condition is a very serious one, as he is very helpless; but such cases have recovered, even when the helpless condition has persisted for several weeks. The involvement of the muscles of respiration necessarily renders the case still more grave, and both the intercostals and the diaphragm are frequently affected in this malady. The affection of these muscles is a common cause of death, owing to the development of pulmonary complications, as a result of their inefficient action. Cases in which the palsy is widespread, involving the limbs and trunk, but where it is not very severe in degree, so that weakness rather than obvious palsy is present, are extraordinarily apt to be overlooked and classed as functional or neurasthenic in origin. They may even be suspected of malingering. Such cases, however, may really be very serious and even fatal, as sometimes the palsy increases rapidly, and death has occurred in more than one case where twenty-four or forty-eight hours before no suspicion of the presence of grave organic disease was entertained. Facial paralysis is also a most characteristic feature of the malady, and it is quite exceptional for it to be really absent, although it may at first escape observation, unless specially looked for. This arises from the fact that the palsy

is usually rather a general weakness of the face muscles than a complete paralysis, and especially because it is often bilateral, and hence there is no marked asymmetry of the face.

In the series of twenty cases carefully recorded, facial palsy was specifically noted in seventeen cases. In two cases there is no note, and in only one case is there a definite statement that facial paralysis was not present at the time of examination. In five cases the facial palsy was unilateral when first observed, and in two of these it subsequently became bilateral. In twelve cases it was bilateral at the time when the patient was first seen; thus, in fourteen out of the seventeen cases the palsy was known to be bilateral in its distribution at some period of the illness. When bilateral, it is not necessarily equally well marked on the two sides of the face. The palsy is of the well-known infranuclear type, involving both the upper and lower portions of the face; thus a very typical sign of the disease is the partial or complete inability to close the eyes firmly, either voluntarily or during sleep. It is most important to recognize that the facial palsy, although nearly always, if not always, present, is usually a weakness rather than a complete palsy. Thus the paralysis is not usually as marked as that seen in Bell's palsy, or in hemiplegia, but it is usually sufficiently marked to cause some difficulty in drinking, and also to cause some eversion of the eyelid and consequent running from the eyes. The patient may also complain of an abnormal feeling on one or both sides of the face. There is no real difficulty in detecting and demonstrating the facial weakness, provided that care is taken in the examination and the bilateral character of the affection is borne in mind, so that its existence is not overlooked owing to the absence of obvious facial distortion.

The onset of the facial palsy is often distinctly later than that of the limbs and trunk; thus a patient may notice the weakness of the legs first, then later that of the arms, and then still later that of the face. In such cases the interval between the involvement of the face and the onset of the limb palsy has been as long as four days. Similarly, in the cases where the facial palsy was at first unilateral, there was a distinct interval of several days before it became bilateral; in one of these cases, under observation the whole time, the interval was three days.

In most cases it has not been possible to determine with certainty whether the facial palsy is subsequent in its origin to that of the limbs and trunk, inasmuch as the patient is so often unaware of its existence, and when the patient has come under observation the face and limb palsy are both present. In the small number of cases that happened to be under observation at the time of the onset of the palsy, there has been a distinct interval varying between two and four days. The facial palsy may not only occur later than the limb palsy, but in cases that improve and recover it may subside before the recovery of power in the limbs is at all complete. The loss of power in the limbs, trunk, and face is the most constant and characteristic feature of the disease, but palsies of other parts occur not infrequently and are sometimes very marked.



Thus difficulty in swallowing, more especially of solids, is not uncommon, and may sometimes give rise to considerable anxiety; it would seem to be dependent upon palsy affecting the pharyngeal muscles. The palate, on the other hand, is only involved in exceptional instances, but sometimes a nasal voice and a difficulty in the swallowing of liquids, similar to that seen in diphtheritic paralysis, may occur.

Paralysis affecting the oculomotor nerves is decidedly rare, and the only ocular nerve affected in this series of cases was the sixth nerve, and this only in one case. No instance of any paralysis of the third or fourth nerve has fallen under the observation of the writer, and thus ptosis has never been seen.

The larynx and tongue have occasionally been affected, and in one case the symptoms were marked and sufficiently akin to those of labio-glossolaryngeal paralysis as to have led to this diagnosis being made prior to the admission of the case to hospital.

The main characteristics of the motor paralysis may be shortly summarized as follows: The palsy is of sudden onset and widespread, affecting more especially the large muscles of the limbs and trunk, but not exclusively limited to them. The face is almost always affected, and generally on both sides. The palsy does not pick out individual muscles or groups of muscles, and hence the limbs and trunk are affected as a whole. Although the palsy is symmetrical, the degree of involvement of the two sides is not always equal. The palsy is practically always progressive in character, and it may conform to the ascending type. Muscular wasting is not a feature of the disease, and in most cases is absent. In some of the more severe cases of prolonged duration, some general wasting of the limbs may be apparent during convalescence, and in one case only there was some atrophy of the muscles of the shoulder-girdle. No case with contracture or even with persistent disability from muscular atrophy has been seen. Some fibrillary twitching of the tongue and of the facial muscles has been seen, but quite exceptionally, and never very pronounced. In some cases curious remissions in the degree of palsy present may occur, so that an apparent improvement may take place one day, and subsequently this disappears and may even be replaced by increased weakness. This misleading and temporary improvement may be seen in cases that are severe and ultimately fatal.

No observations on the electrical reactions of the nerves or muscles were made.

#### *Sensory Phenomena.*

Although the most striking feature of the malady is the widespread and peculiar palsy, the disease is not one that affects the motor functions alone; sensation is also markedly and constantly affected. As mentioned above, the onset of the palsy is apt to be accompanied by such sensory phenomena as pain, numbness, and tingling. The pain is more especially felt in the back, sometimes in the neck, and in some cases in the abdominal and chest walls and in



the limbs. If these are involved the pain is apt to be referred to the joints, e.g. the knees. Headache is also very constantly experienced at the onset of the palsy. The numbness and tingling are felt in the parts subsequently involved in the palsy, but whereas the palsy affects more especially the proximal segments of the limbs, the numbness and tingling are felt especially at the periphery, e.g. the tips of the fingers and toes.

When the face is involved there is often numbness, or numbness and tingling of the face and also of the hips at the onset of the facial palsy. Anaesthesia and analgesia are present, especially in the distal segments of the limbs. The sole of the foot is often affected, and very commonly the distribution of the sensory loss is of the glove or stocking type; but this is not always so, and it may involve areas on the arm or leg corresponding to the cutaneous distribution of the spinal roots, and these areas may be very symmetrical in opposite limbs. It is usual for the sensory loss to be incomplete, relative rather than absolute. A few observations were made on the sense of temperature, with no very conclusive results beyond the fact that there was no evidence of any serious diminution in the appreciation of gross differences of temperature. A sharp line of demarcation may be found in the limbs, limiting the upper level of the sensory loss. No marked sensory loss has as yet been observed on the trunk, but the face may be affected. Just as remissions in the severity of the palsy may occur, so also there may be similar remissions in the extent of the sensory loss, and the boundary line, separating on a limb the area of normal sensation from the area where sensation is diminished, may vary in position in one and the same case, on different days.

Herpes has not been seen either in the areas of the body wall where the patient has complained of pain, or in the analgesic areas having the general distribution of spinal root cutaneous areas.

#### *Reflexes.*

The so-called tendon reflexes of the type of the knee-jerk are lost in all cases where the declared disease has produced marked motor palsy and sensory loss, but if a case is seen and examined at the time of the onset of the palsy, the knee-jerk may still be brisk at a time when the muscular weakness is such that the patient is unable to stand without assistance. In such a case the knee-jerk is lost later, and generally within a few hours of the previous examination. In cases that are not only progressive, but also more or less of the ascending type, the ankle-jerk may be absent when the knee-jerk is still present. All the tendon reflexes, however, such as the ankle-, knee-, wrist-, and elbow-jerks, are soon lost and remain absent for a prolonged period of many weeks.

The superficial reflexes vary; thus the plantar reflex is usually lost, but the abdominal and cremasteric reflexes may be retained in cases where the involvement of the trunk is not very marked. Further, the abdominal reflexes may be present in a case where the trunk weakness is such as to cause difficulty in

turning in bed. In most cases the abdominal reflexes are still present at the stage when the palsy involves mainly the lower limbs and at a time when the knee- and ankle-jerks are lost. Subsequently, with the further progress of the case and the increased affection of the trunk, the abdominal reflexes are also lost. The pupillary reflexes are not affected and the pupil reacts normally both to light and accommodation.

The palatal reflex is also usually normal.

#### *Sphincters.*

The functions of micturition and defecation are not profoundly affected in this malady, and even in the most severe and fatal cases they may remain normal up to the end. In a fair proportion of cases, however, there may be at some time, and more especially soon after the onset of the palsy, some temporary and slight retention of urine; such cases may require catheterization on one or two occasions. No case requiring continued or repeated catheterization has fallen under the observation of the writer. Defecation may be rendered difficult owing to the weakness of the abdominal muscles, but no other disturbance of this function has been observed.

#### *Cerebral Functions.*

These are not obviously affected. In one case the patient was certainly rather drowsy and inclined to sleep unduly; thus he slept the greater part of the day, but he was readily and easily roused and answered all questions quickly and with intelligence. No case with stupor, delirium, or convulsions has been observed, and, speaking generally, the special senses have not been affected. In one case there was some loss of taste and some slight impairment of vision, and the examination of the fields of vision showed the presence of a central scotoma in the left field. The patients always retain full consciousness, and this is so even in the fatal cases where consciousness may remain until the end, as it is not uncommon for death to be sudden. It is perhaps important to emphasize the fact that no cerebral or mental symptoms occur even in the fatal cases.

#### *Cardiac Phenomena.*

In a certain, but probably small proportion of cases, some degree of tachycardia may be present both during the earlier stages of the palsy, when fever is a symptom, and also later, when pyrexia is absent. This occurrence of tachycardia is of some importance, as in several cases it was the cause of serious error in diagnosis, the tachycardia being obvious, and the palsy taking the form of generalized weakness rather than actual paralysis; such cases have in several instances been diagnosed as suffering from disordered action of the heart, so-called

D.A.H., with neurasthenia. The serious nature of the case has thus been overlooked, and such cases have sometimes been fatal, death having occurred with great suddenness. The tachycardia is usually moderate, the most extreme case observed being one where the pulse-rate was 160, with a temperature of 102°. More usually the pulse-rate is between 100 and 120, with a normal temperature, and with the patient lying quietly in bed. The pulse-rate is, of course, greatly quickened if the nature of the case is not recognized, and the patient is allowed to get up and try to exert himself in spite of the physical weakness present. No disturbance of the cardiac rhythm other than tachycardia has been observed, except as a terminal phenomenon shortly before death, when irregularity of the cardiac beat has been noticed.

#### *Urine.*

A small quantity of albumin is often present in the urine even when pyrexia is absent and no catheterization has taken place, but no clinical evidence of any appreciable nephritis, as shown by the presence of blood, casts, &c., has been obtained.

#### *Blood.*

A moderate leucocytosis is present during the early period of the paralytic stage of the disease. The number of white cells has varied between 12,500 and 19,000 per cubic millimetre in different cases. No abnormal cells have been seen, and differential counts have not yielded any very striking departure from the normal. The polymorphonuclear cells have varied from 61 per cent. to 82 per cent. of the total cells, and the lymphocytes from 18 per cent. to 37 per cent. There has been no special increase in the large mononuclears, and no notable change in the number of eosinophils. Further observations on the cell-counts in the blood are required, but the presence of leucocytosis was one of the factors that suggested the probability of the malady being really an infection.

#### *Cerebro-spinal Fluid.*

This has been examined in four cases, the fluid being obtained by ordinary lumbar puncture. In all cases the fluid has been quite limpid, free from cells, and no abnormality, not even an increased quantity under pressure, has been observed.

The Wassermann reaction was determined in two cases and was negative in both instances.

#### *Course of the Disease.*

The progress of these cases, even when they improve, is usually slow, but perhaps the most striking feature is the rapidity with which urgent symptoms and death are apt to develop in cases that do not present any symptoms giving

rise to anxiety at the time they are first examined. Thus cases may be seen where there is perhaps a widespread palsy or weakness of the trunk and limbs, but where neither the state of the respiration nor that of the pulse suggests the imminence of danger, and yet such patients may die with great suddenness within twelve hours of the examination. The mortality of the disease is high. Thus in the series of thirty cases death occurred in eight. In six of these cases the date of the onset of the palsy could be ascertained, and the time at which death occurred was as follows: in two cases death took place on the fifth day, in one case on the sixth day, in one case on the eighth day, in one case on the eleventh day, and in one case on the twentieth day. Thus half the deaths occurred within a week of the onset of the palsy, and only one death took place after the eleventh day. In half of the fatal cases there was considerable respiratory embarrassment, often dependent upon obstruction of the bronchi with retained secretions, or with the presence of some inflammatory pulmonary complication. In the other fatal cases death was more sudden, and although possibly really dependent upon respiratory failure, it was not associated with gross pulmonary lesions. In these fatal cases, oedema of the brain and general visceral congestion were the only marked naked-eye lesions present on post-mortem examination.

In the cases where recovery ultimately took place, the palsy, after being progressive, became stationary, and then began slowly to improve. The palsy of the face sometimes improved first, and then there was a gradual and slow return of power in the trunk and limbs. In severe cases the progress is always slow; thus in one case the onset of palsy occurred on June 9, 1917, and the patient was only fit to be evacuated to England on August 6, and although two months had elapsed the weakness of the limbs was still quite obvious. In another case, where the palsy was first noticed shortly before August 20, 1917, the patient was evacuated to England on September 29, when, although there had been a great improvement, there was still weakness of the face, trunk, and limbs. On January 8, 1918, he was examined and found to be quite well, able to walk well, and no signs of any lesion of the nervous system could be detected, and the knee-jerks had returned and were normal. This case was one of great severity, with double facial palsy, profound involvement of the trunk and limbs, together with considerable tachycardia, and his condition caused considerable anxiety for many days, owing to the weakness of the muscles of respiration, including the diaphragm. No case has been evacuated until there was a very marked and general improvement in the palsy, since so long as this is present in the trunk muscles to any material degree there is grave risk of respiratory embarrassment, with the possibility of sudden or rapid death. In cases of a severe type it would seem that a period of about two months elapses between the onset of the palsy and a degree of recovery that renders evacuation feasible, and that a period as long as six months may be necessary for the patient to regain his usual health.

*Complications.*

The only complications observed in this series of cases have been certain affections of the respiratory system, presumably dependent upon the palsy of the respiratory muscles, since both the diaphragm and the intercostal muscles are liable to be involved. The impaired respiratory movements necessarily lead to the retention of secretions in the bronchi, and thus the lungs become clogged to a greater or less degree. Further, extreme congestion of the lungs is a common post-mortem phenomenon, and this, doubtless, is also dependent upon the inefficient aeration and impaired expansion of the lungs. Bronchitis and broncho-pneumonia are also not uncommon, and, although very serious, are not necessarily fatal. In some cases there is great respiratory distress, together with the expectoration of a viscid blood-stained sputum, brought up with much difficulty owing to the muscular weakness, but not accompanied with pyrexia or any great acceleration of respiration. This condition is probably dependent rather upon extreme congestion and retention of bronchial secretion than upon actual pneumonia. Dry pleurisy may also occur. In view of the marked weakness of the respiratory muscles, it is rather remarkable that no case of massive collapse of the lung such as that described in fatal cases of diphtheritic neuritis has been observed.

Death would seem to be due to respiratory failure, this failure being dependent upon the muscular palsy. It is, of course, possible that it may not always be of peripheral origin, and that sometimes it may have a central origin and be due to failure of the nerve centres. It is certainly very remarkable how suddenly death may occur without the previous development of any obvious signs of deficient aeration of the blood, such as cyanosis, &c. This has been so in half the fatal cases, but equally sudden deaths are known to occur in various conditions where it is certain that the respiratory failure is dependent upon mechanical and peripheral causes, more especially in several affections of the upper respiratory tract, e.g. inflammatory affections of the larynx. In the remaining fatal cases the respiratory failure is gradual and progressive and dependent upon the development of the pulmonary complications mentioned above. The mortality in the whole series of thirty cases was 26.6 per cent.

*Post-mortem Observations.*

Autopsies were made in seven out of the eight fatal cases. No gross lesions in the nervous system were ever seen, but in some cases the brain seemed somewhat oedematous, and some congestion of the vessels was occasionally present. The spinal veins between the dura mater and the vertebral column were often greatly distended. The lungs showed great congestion, and subpleural petechial haemorrhages were not infrequent. Bronchitis, broncho-pneumonia, and plastic pleurisy were sometimes present. The mediastinal glands were sometimes enlarged and soft, but no general glandular enlargement was observed. No



lesion beyond marked congestion of such viscera as the liver and spleen, and great congestion of the veins generally, was seen. The kidneys showed no naked-eye changes suggestive of nephritis.

### *Aetiology.*

The youngest age at which the disease has been seen is 19 years and the oldest 49 years. Nearly half the cases, i. e. nine out of twenty, occurred in men under 25 years of age, and only three out of twenty in men older than 35. Nineteen out of the twenty cases were observed during the year 1917, and only one case in 1918, but owing to a variety of circumstances no great stress can be laid on this observation. Nine of the twenty cases occurred during the winter months—three in January, four in November, and two in December. In June, however, there were also four cases. The remaining seven cases occurred as follows: two each in July and September, one each in April and May 1917, and one in April 1918. It is not really possible to draw any deductions as to seasonal incidence from these figures, owing to the small number of cases and the very large area from which they were drawn. It is clear, however, that only sporadic cases have occurred, and there is no evidence of any epidemic outbreak, although it is very probable that the real number of cases is much larger than the record given alone would suggest, as the malady may readily be overlooked, and it is also very probable that there are mild cases where the diagnosis would always be difficult and very often impossible. The writer has seen several cases where facial palsy was present and the patient complained of a vague weakness in his limbs, and others where, after an initial short illness of vague character, the patient had complained of general weakness and the knee-jerks were found to be absent. It is quite possible that there are really instances of mild attacks of the same disease as that here described, but, as already mentioned, only typical cases have been so far considered. It should be mentioned here that the Klebs-Loeffler bacillus has never been found in bacteriological examination of the throat in any case in the series here described.

### *Discussion of the Clinical Features of the Malady.*

The clinical picture presented by this series of cases, although resembling in some respects that seen in certain well-recognized varieties of neuritis, yet, on the whole, differs in many important respects, and so would seem really entitled to recognition as a distinct clinical entity. The remarkably constant bilateral affection of the face is a very striking feature of the disease, as is also the involvement of the muscles of the trunk. Further, the presence of generalized weakness rather than of actual paralysis of individual muscles or groups of muscles is very characteristic. Again, the progressive nature of the palsy, and its occasional ascending character, together with the curious manner in which the proximal segments of the limbs with their large muscles are mainly involved, are all



striking facts in this disease, and are not, at any rate, familiar observations in other affections of the nervous system. The involvement of sensation, as well as of motion, causes of course some resemblance between this so-called polyneuritis and other well-recognized forms of neuritis. The absence of obvious muscular atrophy and of other trophic lesions would not militate against the malady being a neuritis, since such effects are often absent in such a well-recognized variety of neuritis as that seen as a complication of diphtheria, and it must be admitted that so-called polyneuritis presents several points of resemblance to diphtheritic neuritis. The constancy of bilateral facial palsy, with the rarity of oculomotor and palatal palsies in the one disease, whereas in the other the exact converse holds, would seem to afford a very sharp distinction between the two diseases, and the resemblance of this malady clinically to diphtheritic neuritis is closer than to any other form of neuritis, including beri-beri. If it is to be regarded as a neuritis, it would have to be separated off from other varieties and looked upon as a special type of neuritis with a definite and very constant clinical picture. If, however, the results of the study of the morbid anatomy of the disease and the facts acquired by the experimental study are also taken into consideration, it does not seem necessary to discuss further this portion of the subject, as these results show clearly that the malady is quite distinct from any known form of peripheral neuritis. As soon as direct experiment proved that the malady was communicable to the monkey by the subdural inoculation of glycerinated spinal cord derived from fatal human cases, the question of the relationship of the disease to poliomyelitis naturally arose. A polyneuritic variety of poliomyelitis has been described, although such cases have not presented the remarkably uniform clinical picture recorded in the present series of cases. Cases of poliomyelitis have been extremely rare in the troops of the British Expeditionary Force, and the writer has seen very few cases during a period of nearly four years whilst acting as consulting physician to a large number of hospitals. If the cases of so-called polyneuritis are really instances of abnormal or rare forms of poliomyelitis, it would be expected that the ordinary form of the disease would also be prevalent and would be met with in larger numbers than the supposed rare form. Such, however, is not the case, and all the cases of so-called polyneuritis not only present a remarkably uniform clinical picture, but are not associated with any symptoms or signs of ordinary poliomyelitis either in themselves or in others. Poliomyelitis is characterized, amongst other features, by the sudden affection of one or more groups of muscles; the lesion is not a progressive, still less an ascending one, and contracture, atrophy, and deformity are all well-recognized and common sequelae. In polyneuritis, on the other hand, these are all absent, while sensory loss is common, if not invariable.

The results of the experimental and bacteriological investigation of polyneuritis undoubtedly show that the malady has affinities with poliomyelitis, but they also show that the two diseases are not identical. This, for instance, is well seen in the study of the histology of the morbid lesions. The bacteriological results show the presence of a virus presenting several points of resem-

blance to that isolated by other observers in cases of poliomyelitis. The distribution of the lesions in the nervous system of man and of the monkey also resembles that characteristic of poliomyelitis, but not closely. There are thus very distinct differences in the two diseases, both in the morbid anatomy and in the morphology and cultural characteristics of the virus. It is significant that this should be so, inasmuch as there are also, as pointed out above, quite marked clinical differences in man between this malady and poliomyelitis.

In the presence of these facts, the conclusion would seem to be justified that so-called acute febrile polyneuritis is really a malady allied to, but quite distinct from, poliomyelitis. This conclusion would entail as a corollary that the virus of poliomyelitis, instead of being an isolated and peculiar virus, is really one member of a class of organisms, and that the virus of polyneuritis is another, but distinct member of this class.

It is obvious that much further work will be necessary to substantiate this theory, and especially a thorough and systematic comparative study from the experimental side of the virus of poliomyelitis on the one hand, and that of polyneuritis on the other. This study should also include conditions thought to be allied to poliomyelitis, such as encephalitis in some of its forms. In the meantime, the results detailed in this paper would seem to justify the following conclusions:

1. So-called acute febrile polyneuritis is a very definite entity, capable of being separated clinically from other diseases of the nervous system.
2. It is a diffuse affection of the nervous system affecting the spinal cord, spinal ganglia, and peripheral nerves, with but a slight incidence on the cortex.
3. The lesion is essentially one affecting the nerve elements, cells, and fibres.
4. The malady can be transmitted experimentally from man to the monkey, and the characteristic lesions reproduced in the experimental animal.
5. A living virus can be shown to be present, both in the human cases and in the inoculated monkeys.
6. The disease can be produced in the monkey by the suitable inoculation of the virus in pure culture, and the virus can be recovered from such experimental animal.

#### REFERENCES.

1. Osler, *Principles and Practice of Med.*, New York and Lond., 1916, 8th edit., 1022-3.
2. Holmes, Gordon, *Brit. Med.*, July 1917, ii. 37.

## PART II

## THE MORBID ANATOMY OF THE DISEASE IN MAN AND IN THE MONKEY, TOGETHER WITH THE EXPERIMENTAL PRODUCTION OF THE DISEASE IN THE MONKEY

BY E. F. BASHFORD

Early in June 1917, Major-General Sir John Rose Bradford brought me some tissues, with the request that I should preserve the spinal cord and salivary gland in 50 per cent. glycerin, and thereafter inoculate a few drops of an emulsion of the cord and gland in saline subdurally into rabbits, following the procedure he had himself used many years ago at the Brown Institution, when engaged on the investigation of rabies in England before its abolition and exclusion from the country. At the same time he suggested the examination of the tissues, especially of the nerves, for evidence of acute neuritis, and of the cord for any lesions of the nerve-cells. These preliminary inquiries were carried out as well as the facilities of active service permitted. At a later date, indeed, so soon as the reproduction of the clinical course and of the several lesions observed in man had been demonstrated by the transmission of the disease to monkeys, the spinal cords of the earliest and later cases still preserved in glycerin were given into the hands of Capt. J. A. Wilson, R.A.M.C., for bacteriological investigation. Towards the end of July 1917, Col. Gordon Holmes published in the *British Medical Journal* a brief account of apparently similar cases, together with such histological examinations as he had been able to make; so far as his admittedly limited histological descriptions went, they agreed with the conclusion that the disease was a form of neuritis differing from that found in metallic and alcoholic poisoning. Col. Gordon Holmes's descriptions, where they covered the more extensive ground of the material already collected for this investigation, agreed with the findings based thereon, but without his raising the question of the possibly infective nature of the disease. The subsequent course of the investigation is set forth below.

*Post-mortem Examinations.*

Of the fatal cases, six came to careful examination in the mortuary. The reports of Capt. T. G. H. Shore, R.A.M.C., the officer in charge of the mortuary, for two cases is as follows:

*Case II. Head.* Cyanosed face. Great congestion of dural vessels. Great oedema of pia-arachnoid. A little ventricular distension. Small congested vessels visible in white matter. No other abnormality present.

*Cord.* Marked distension of theca. Engorgement of veins. An area of softening in mid-dorsal region (found on histological examination to be injury inflicted at opening of spinal canal.—E. F. B.).

*Lungs.* Marked emphysema on both sides. Some engorgement and collapse at right base.

*Heart.* Somewhat dilated—old pericardial thickening.

*Liver, spleen, kidneys.* Congested.

*Death.* Polyneuritis. Oedema of brain. General congestion. Softening of cord (see note above).

*Case III.* Subcutaneous oedema lower back, also in muscles of lower back.

*Thorax.* Right lung very adherent, old scar external surface, numerous small subpleural pin-point nodules—? tubercles. Left lung: large scar external surface upper lobe, numerous fine tubercles. Broncho-pneumonia.

*Heart.* 12½ oz.

*Kidneys.* Right 9½ oz., left 9½ oz. A small subcapsular haemorrhage on each kidney, more marked on right.

*Spleen.* Negative.

*Death.* Broncho-pneumonia. ? Nephritis.

Of the other cases, it is noted for Case I: Dura mater very adherent in places. For Case IV: Nothing of note. For Case V: Diagnosis pneumonia, polyneuritis. Right kidney, 9½ oz. Left kidney, 9½ oz. Heart, 12½. Kidneys showed subcapsular haemorrhage. Lung, ? T.B. Case VI: Liver, 7 oz. Heart, 12 oz. Kidneys, 5 and 5½ oz. Spleen, 7½ oz.

It may be stated, therefore, that the post-mortem examination yielded no crude or adequate explanation of the course of the nervous symptoms. The congestion of the meningeal vessels was not a constant finding; indeed, the *sectio cadaveris* of itself did not explain the fatal issues.

#### *Histological Examinations.*

*Material.* The tissues preserved for histological examination were chosen at first in a somewhat haphazard way, owing to the absence of any guidance beyond that afforded by the very definite clinical evidence of neuritis and respiratory paralysis. Tissues from the six fatal cases were preserved in formalin (10 per cent.) and in Zenker's solution as follows:

18.6.17. *Case I.* Cortex. Pons. Medulla. Sciatic, posterior tibial, and phrenic nerves. Liver, lung, kidney. The salivary gland and cord were placed in 50 per cent. glycerin, and the cord thus preserved was subsequently examined histologically after hardening in formalin.

29.6.17. *Case II.* Cortex. Pons. Medulla. Spinal cord (cervical and lumbar enlargements mid-dorsal). Sciatic, anterior tibial, and phrenic nerves. Pituitary.

24.7.17. *Case III.* Cortex. Medulla. Cord. Cervical and lumbar enlargements mid-dorsal. Sciatic, posterior and anterior tibial, vagus, and phrenic nerves. Kidney, liver, quadriceps and gastrocnemius muscles.

5.8.17. *Case IV.* Cortex. Medulla. Cord (cervical and lumbar enlargements). Phrenic, vagus, anterior and posterior tibial nerves.

26.9.17. *Case V.* Cortex. Cord (whole). Sciatic and phrenic nerves. Kidney, liver, lung, heart, muscle.

4.5.18. *Case VI.* Whole brain. Cortex. Medulla. Cord (whole). Sciatic, phrenic, radial, and musculo-cutaneous nerves. Salivary gland, lymphatic glands. Diaphragm, muscles, liver, kidney, spleen.

To this material there was added for comparison tissues from four other obscure cases of nervous disease occurring during the same time.

(a) A case of syphilis. Cortex. Medulla. Sciatic, anterior and posterior tibial, and phrenic nerves. Liver, kidney.

(b) An anomalous case arriving moribund at the base. Cortex, cord, various nerves. Liver, kidney, heart, lymphatic gland.

(c) A case of acute myelitis. Whole brain, cord, sciatic and radial nerves. Salivary and lymphatic glands. Liver, kidney.

(Streptococci and staphylococci were recovered by culture from softened areas in the cord, and on injection (subdurally) into rabbits were recovered from the blood stream without nervous symptoms developing.)

(d) *Col. Pasteur's Treport Case*. Whole brain and cord hardened by injection of 5 per cent. formalin into carotid artery.

(e) In June-July 1916 two typical fatal cases of anterior poliomyelitis came under observation, and with them three other non-fatal cases were found associated and arising in the same billets. Notwithstanding every effort made to trace possible cases of acute or subacute anterior poliomyelitis during 1917-18, and an open appeal to medical officers to report any suspicious cases, not one such case was reported during the period in which the above six fatal cases occurred.

#### *Methods.*

These have been of necessity much restricted. All material was examined after hardening in formalin and Zenker's solution. Large numbers of serial sections were examined after staining with Harris's haematoxylin and eosin, or by eosin and methylene blue, as described by Mallory, and differentiating with colophonium. The latter gave the most beautiful preparations and stains Nissl's granules well; but, unfortunately, under the conditions of active service, they do not keep, either owing to impurity of the stains or the bad quality of the Canada balsam. For special purposes phosphotungstic acid-haematoxylin or Weigert's iron-alum-haematoxylin were used. Unfortunately, the materials for carrying out Nissl's stain were not available, nor could the other more delicate methods of staining the central nervous system be applied. Tract degenerations have not been studied. The spinal cord of the first case had been placed in 50 per cent. glycerin by General Sir John Rose Bradford, with a view to inoculation on analogy with paralytic rabies. After subsequent hardening of a portion in formalin it was examined histologically at the same time as Case II, with which, allowing for the imperfect preservation, the findings agreed.

#### *Naked-eye Examination.*

From the post-mortem records it will have been observed that gross lesions of the nervous systems, and indeed of all the organs, such as would explain the clinical symptoms and course of the disease, were absent. The only finding at autopsy was congestion of the meningeal vessels, with some oedema of the central



nervous system which may well have been terminal and associated secondarily with respiratory embarrassment. After hardening in formalin and in Zenker's solution the cord showed in cross-section minute petechial haemorrhages and great engorgement of the meningeal vessels in Case II, together with an inequality in the size and shape of the grey matter of either side of the cord, varying in degree at different levels in the cervical and lumbar regions (see Pl. 3, Figs. 1 and 2). There was otherwise absolutely nothing attracting the attention of the unaided eye (see also Pl. 7, Fig. 13).

*Microscopical Examination. General Survey.*

It has not yet been possible to examine exhaustively the large amount of material collected. From the first two cases a very large number of serial sections was made from the several tissues preserved. It was first of all ascertained that there was evidence of acute neuritis in the sciatic nerve (see Figs. 3 and 4). The examination of the spinal cord under low magnification revealed at first nothing more than minute and widely diffused haemorrhages in the dorsal enlargement, and an excessive and diffuse interstitial cellularity in both the cervical and lumbar enlargements. The round cells were not accumulated around the branches of the meningeal vessels, which were surrounded by open clear spaces. The central neural canal showed considerable proliferation of the ependymal cells. It was only when attention was concentrated upon the nerve-cells themselves that pathognomic lesions were noticed. In sections at one level of the cervical enlargement it was noted that the cells of one anterior horn appeared normal, while those of the opposite side were apparently greatly reduced in numbers, and closely surrounded by a small round-celled infiltration. At another level this relationship was reversed. This disturbance of the nerve-cells was not limited, however, to the anterior horn, but involved also the posterior columns and the tract-cells. Similar pathological changes were evident in the lumbar enlargement. While the left anterior horn of the cervical enlargement might show little change, the right horn showed much, the changes in the posterior horns being reversed (see Figs. 1 and 2). In the dorsal enlargement the left anterior horn showed more change than the right, and the nerve-cells in the left posterior horn were also more affected (Fig. 2), quite apart from the more extensive congestion and numerous haemorrhages in the dorsal region. Indeed, the irregular distribution of the nerve-cell lesions in both enlargements was a very striking feature. This irregularity remained a characteristic feature in a long series of serial sections; it was not possible in the course of their examination to determine that the lesions picked out any one particular area in the grey matter of the cord. These general features were characteristic of all six fatal cases examined. Case I may be left out of further consideration so far as the cord is concerned, because the material had been kept for some days in glycerin before hardening in formalin.



*Microscopical Examination: Minute Details.*

*Nerves.* All the nerves examined showed similar features, but of varying intensity in the six cases, and always more marked in the nerves from the lower limbs. For purely sensory nerves like the radial and the musculo-cutaneous, many sections had to be examined before the features readily found in the sciatic, posterior and anterior tibial, or phrenic were clearly demonstrated. Wallerian degeneration was always present, and more extensively evident on staining by osmic acid than by Marchi, which, of course, only reveals the older lesions. It was accompanied by the usual proliferation of the cells of Schwann. The Wallerian degeneration was, however, never massive; it picked out isolated fibres or even groups of fibres, leaving others entirely free. It was accompanied by an acute neuritis, with an inflammatory exudate of round cells and haemorrhages (Figs. 3 and 4). This neuritis was not uniformly distributed throughout the nerves, not even in the sciatic, where it was always most easily detected. It affected only little areas here and there, being sometimes most marked towards the centre of a nerve trunk, and sometimes more so under the sheath. On transverse section and staining by osmic acid or Marchi, the radial arrangement of the medullary sheath was seen to be disturbed or lost, and there were dots and complete or partial rings of degeneration. Sometimes the medullary sheaths were merely greatly swollen. The axis cylinders were sometimes swollen and irregularly stained and fragmented, at other times not. The non-medullated fibres appeared relatively exempt as contrasted with the medullated. These changes were particularly interesting in the case of the phrenic and vagus nerves (Figs. 5 and 6).

*Spinal cord.* It was only after attention was focused on the nerve-cells of the spinal cord that far-reaching, if minute and purely cytological, lesions were observed. Only the earliest stages were seen in Case VI, where they were limited to eccentricity of the nucleus in the majority of the tract-cells, in some cases combined with swelling of the nucleus, in others along with a considerable departure from its normal circular outline, the latter giving place to an undulating and at times almost crenated outline. The nucleolus remained either central or was displaced, so as to be almost adjacent to the nuclear membrane. In a few of the tract-cells the nuclear membrane failed to show up. The processes running out from the tract-cells stained of an unusual depth with haematoxylin and methylene blue, and in some cases irregularly, owing to clumping of the tigroid substance. The tigroid substance in the body of the nerve-cells would not have attracted much attention, had it not been for the more marked changes observed in the Cases I to V. An occasional tract-cell was more widely degenerated, much shrunken, and retained both the methylene blue or haematoxylin and eosin irregularly without a clear differentiation of cytoplasm and nucleus. There was a slight diffuse round-celled infiltration of the grey matter of both anterior and posterior horns; but no accumulation of these cells either around the vessels or nerve-cells. The ependymal cells of the central canal had proliferated. In

addition to being accumulated around the central canal, they formed strands in the commissure, where the vessels were surrounded by unusually large perivascular spaces. The pericellular spaces, on the other hand, did not obtrude.

In all the other cases the changes in the nerve-cells were more marked. They did not spare the large motor cells of the anterior horn, nor indeed any area of the cord, although they seemed to pick out groups of cells irregularly and varying groups from one section to another. Even the cells of Clarke's column were at times quite seriously affected. A much-degenerated cell might be encountered in a group of healthy cells, or, on the other hand, cells or only one cell remain normal amidst a group of cells showing all stages of degeneration (see Figs. 15 and 17). Such a group of degenerated cells is shown in Fig. 7. The nuclei of three cells are seen to be markedly eccentric and shrunken. In two of them the nuclear membrane is not visible. The nucleus of the fourth cell did not come into this section, but its nucleus was likewise eccentric. The cell bodies will be observed to have lost their typical angular outlines. They have become rounded, in one case with complete loss of the dendritic processes. Occasionally the cytoplasm showed one large or several small vacuoles. The tigroid substance in some cases is clumped, in others powdery, both in the cell bodies and in the dendritic processes. The tigroid substance tended to disappear from the periphery of some cells, but from the centres of others. The axis cylinder sometimes appeared swollen or showed no obvious change. Two of the cells in Fig. 7 show an excessive amount of fat-like yellowish pigment, which stained as brownish granules by Marchi. The pericellular spaces are unusually large, as if in some cases the cell had shrunk away from the interstitial substance. In Fig. 7 the round-celled infiltration shown is slight, and it is not associated with the capillaries. In other areas of the same section, the small round-celled infiltration was more extensive between the cells, but more especially around them, so that many were closely invested and appeared to be undergoing absorption. In such cases the dendritic processes were often broken and likewise closely surrounded by round cells. Then, also, the nerve-cells often presented vacuoles in the cytoplasm, or their outlines were definitely hollowed out, where a round cell was applied; occasionally one or more of the latter had penetrated into the remains of the cytoplasm. Even when there was marked congestion of the meningeal vessels and capillaries, as in Fig. 13, the absence of a cellular infiltration in definite association with them, such as is characteristic of the earlier stages of anterior poliomyelitis, was a striking and interesting contrast to the accumulation of such cells around the nerve-cells. The only instance in which a lesion was found associated with the vessels was Case III, where the capillaries, instead of lying free in a dilated perivascular space, were surrounded by a curious homogeneous (hyaline) substance, broken up into irregular fragments. The same change had affected single or groups of proliferated ependymal cells (Figs. 8 and 9).

The white matter of the cord presented little or nothing to attract attention when stained by ordinary methods. No small-celled infiltration accompanied the

ramifications of the meningeal vessels or pia mater. Even small haemorrhages were very rarely seen. When stained by Marchi, axis cylinders and medullary sheaths were readily picked out, showing the usual features of Wallerian degeneration, as seen in cross-section (Figs. 5 and 6). There was no noticeable increase in the cellularity of the white matter, except in the anterior and posterior roots, which at times appeared excessively cellular, even in the case of the substantia gelatinosa.

*Posterior root ganglia.* In the earlier cases the posterior root ganglia were not specially dissected out and preserved: imperfect specimens from the cervical enlargement only were recovered later, from Cases II, III, IV, and V. The examination appeared negative, except for a little cellularity between the cells of the ganglia, which appeared to be explained more by oblique sectioning than as a pathological process. From Case VI, however, ganglia were specially preserved both from the cervical, dorsal, and lumbar portions of the cord. The lumbar and dorsal ganglia showed a marked contrast to the cervical. Whereas the latter showed little or nothing abnormal, the former showed changes in the nerve-cells. There was eccentricity of the nuclei, almost extrusion in some cases (see Fig. 23), occasionally vacuolation of the cytoplasm. The vacuolation occasionally advanced to a degree which gave the cell and its displaced cytoplasm and shrunken nucleus the appearance of a signet-ring. The tigroid substance was clumped or finely granular and tending to disappear near the periphery of some of the cells. Some cells contained an excess of pigment. Between the cells there was a marked but patchy accumulation of round cells, the nature of which was not evident. The capsule showed nothing abnormal.

*Muscles.* The nerve changes were accompanied by degenerative changes in the voluntary muscles, and here again staining by osmic acid or Marchi showed that individual fibres or groups of fibres were picked out and others spared. One fibre might show quite extensive rows of dots of fat running longitudinally the whole length of the section, an adjacent fibre only a few short rows of minute dots, and yet other adjacent fibres be quite free from degeneration (see Fig. 10).

The examination of the diaphragm and heart-wall has not been completed.

*Brain.* Portions of the motor cortex, posterior lobe, and cerebellum were examined. All showed a slight degree of round-celled infiltration most marked around the large antler cells of the motor cortex, and, on the whole, more evident in the deeper than in the superficial layers of the grey matter. The nerve-cells themselves showed very little change, perhaps a slight eccentricity of the nucleus. In the cerebellum the margin between the stratum granulosum was somewhat more diffuse than normal, owing to the presence of round cells. The Purkinje nerve-cells did not show evident disturbance. A similar state of affairs obtained around the cells of the nuclei of the pons and the neighbourhood of the calamus scriptorum (respiratory centre). Everywhere in the brain the changes were early as compared with the cord, especially in its lower levels.

*Liver, kidney, lung.* The only change in the liver was a slight and variable

infiltration of round cells in the large and small portal tracts such as is found in many febrile (infective) diseases. The kidneys in all cases showed early patchy parenchymatous and glomerular nephritis. The examination of the lungs yielded nothing beyond what was recorded at the autopsies.

*Summary.* The foregoing details amplify in many particulars those given by Gordon Holmes (1), as well as yield a number of new observations, such as the acute exudative neuritis—the involvement of the posterior root ganglia—the haemorrhages throughout the cord—the nature and distribution of the finer degenerations of the nerve-cells, especially of the various groups of tract-cells and those of the postero-lateral column—the general involvement of the grey matter of the brain and medulla—the muscular degeneration—the nephritis and changes in the liver. They indicate clearly a general involvement of the grey matter of the entire nervous system with a gradually ascending progression, and are compatible with neuritis dominating the early clinical features. There are clear indications that the nerve-cells of the cord are involved early, and that the diffuse accumulation of round cells is a later phenomenon to which their aggregation around damaged or degenerated nerve-cells succeeds at a still later stage. Consideration of the whole pathological processes would point to a septicaemia or systemic poisoning, which enters the central nervous system by way of the nerve trunks, both motor and sensory, and probably of an infective nature. The lesions, while recalling and even resembling some features met with in the classical descriptions of those of acute or subacute anterior poliomyelitis, are clearly distinguishable from them, and raise the whole question of 'ascending paralysis' in the widest sense.

#### TRANSMISSION OF THE DISEASE FROM MAN TO MONKEYS.

*Rabbits and guinea-pigs.* Three rabbits were inoculated from Case I with negative results by intravenous, intraperitoneal, and subdural routes with emulsion of spinal cord and salivary gland (mixed accidentally). Cerebro-spinal fluid, obtained post mortem, was injected intravenously and intraperitoneally without result. Cerebro-spinal fluid from a non-fatal case was also injected subdurally in a rabbit without result. The intraperitoneal injection of guinea-pigs with cerebro-spinal fluid or emulsion was likewise negative. It does not follow, as yet, that the disease is not communicable to rabbits by subdural inoculation, since only one experiment has been made up to now.

*Monkeys.* On the other hand, when subdural inoculation was practised after complete anaesthesia had been established by ether on *Macacus rhesus*, positive results were obtained. The cords of three cases, after preservation in 50 per cent. glycerin for 3 months (Case II), 7 months (Case III), and 25 days (Case VI), all gave rise to the disease. Hence the causative agent is very resistant to the action of glycerin, in contrast to the cocci and bacteria with which the material was contaminated at the time when first preserved. The glycerin and

the cord, as well as the emulsion employed, were all sterile on culturing by ordinary aerobic and anaerobic methods at the times of inoculation. Since inoculation from monkey to monkey was also successful, it may be regarded as established that the causative agent is of an infective nature.

*Tables of Inoculation Experiments.*

(1) *Man to Monkey.*

Material in Glycerin.	Monkeys inoculated.	Results.
		All positive.
Case II. 29.6.17 to 1.10.17 (3 months)	1 2	Killed 29.11.17 (8½ weeks) Died suddenly 24.2.18 (16 weeks after first inoculation)
Case III. 24.7.17 to 15.2.18 (7 months)	5	Killed 10.4.18 (7-8 weeks)
Case IV. 4.5.18 to 29.5.18 (25 days)	8* 9	Killed 11.7.18 (6 weeks) Killed 11.7.18 (6 weeks)

\* Monkey 9 was inoculated with the emulsion of preserved cord at the same time as Monkey 8 was inoculated with a culture from same cord as prepared by Capt. J. A. Wilson, R.A.M.C.

(2) *Monkey to Monkey.*

Material.	Monkeys inoculated.	Results.
Emulsion of cord from Monkey 1	2 reinoculated 8.12.17	Died suddenly 24.2.18 (11 weeks after second inoculation)
19 days in glycerin	3 inoculated 8.12.17	Killed 9.7.18 (30 weeks)
Immediate inoculation of fresh cord emulsion from Monkey 5	6* inoculated 10.4.18 7 inoculated 10.4.18	Never any symptoms Still living at 4 months but ill typically since onset at 5-6 weeks

\* This animal was not *M. rhesus*, but a very different species. There was also some doubt if subdural inoculation was properly effected owing to the thickness of skull.

(3) *Inoculation of Culture received from Capt. Wilson.*

Material.		Result.
Culture	Monkey 8	Killed 11.7.18 (6 weeks)

(4) *Inoculation of Filtrate received from Capt. Wilson.*

Material.		Result.
Filtrate 0.5 c.c.	Monkey 10	No symptoms after 6 weeks

From the preceding tables it will be apparent that the transmission of the disease to *M. rhesus* by subdural inoculation of an emulsion of cord is easy. Only a very few drops—at most 0.5 c.c.—of the clear fluid from above the sediments of the three fatal cases was used. In only one monkey (No. 5) was the operation followed by an immediate paralysis of the opposite arm, which was recovered from completely in 10 days. In this instance care was taken, when examining the cord histologically, to exclude any lesion arising in consequence. The other monkeys showed no alteration in their usual behaviour or appetite, after recovering from the anaesthetic, for about a week, when for from 8 or 10 to 14 days they appeared to shiver and certainly lose their appetites, and remained abnormally still, sometimes holding their heads. Some of them



developed a nasal discharge, and one of them diarrhoea. What significance is to be attached to these signs of illness it is hard to say. The monkeys were warmly and roomily housed near an incinerator fire, kept clean, and well fed on a varied diet of roots, fruit, and bread and milk. While in the early cases it seemed as if no significance could be attached to these early signs of illness, in the later experiments one felt inclined to look out for their appearance as characteristic and hopeful of a positive result. These prodromal symptoms passed off and the inoculated could not be distinguished from the uninoculated inhabitants of the monkey-house till about a month elapsed. At this time lassitude reappeared with surprising regularity, together with loss of appetite and an unwillingness to use the hind limbs for jumping, climbing being resorted to for preference. One hind limb might be evidently more affected than the other, or the monkey employed one or both hands to steady itself on a perch, on which it had formerly sat securely without any such aid. Usually there was evidence of extensor weakness, e.g. one or both feet pointing, or even a definite trailing of one limb. The development of these symptoms was not sudden but very insidious, although always well marked in 5-6 weeks. Usually within a week or fortnight after the first definite signs, the arms became similarly involved, either bilaterally, so that the animal would only take any food proffered by seizing it in the mouth and not offer to use its hands. Only one hand would be used in eating, the other showing perhaps a typical wrist-drop. If one of the hands was used tremors were present. Ultimately the muscles of the jaw were affected in two cases, and only soft food would be accepted; the animals exercised very little pressure on a finger inserted between the teeth, and did not attempt to bite. The eyelids were not noticed to be affected nor the pupils. In one instance (Monkey 1) the animal gradually got so bad that it could not hold up its head for long. After sleep, the face was puffy and oedematous, the oedema gradually descending from the face to the neck after awakening. It seemed that the monkey must die. Its respiratory movements, while very shallow, appeared normal, and, so far as could be judged, the diaphragm was acting on the lower ribs. Notwithstanding its parlous state, the monkey, to one's surprise, began to get well, with ups and downs, and at 8½ weeks it was killed, lest what had been attained should be lost in a complete recovery. This, indeed, appeared to occur for Monkey 2, inoculated at the same time, in which the symptoms, while quite definite, never extended beyond the hind limbs to such an extent as to be easily noticeable. At the worst this monkey never ceased to be able to use its arms for climbing, and in feeding used only the right hand. By the time the first monkey was killed, the second appeared to have all but completely recovered,<sup>1</sup> which fact largely influenced the decision taken as regards Monkey 1. Monkeys 8 and 9 were interesting because they were inoculated at the same time, No. 8 from culture prepared by Capt. Wilson, No. 9 from the cord of Case VI, from which the culture had been made. The symptoms were

<sup>1</sup> The monkey (No. 2) which appeared to recover was again inoculated with emulsion from the spinal cord of Monkey 1. See later.



evident earlier and more marked in Monkey 8, which was inoculated with culture. After a month there was slight muscular weakness, it climbed rather than jumped, there was drooping of the right hind foot and tremors in muscles of right thigh. Monkey 9 was able to leap across the cage, but unable to grasp the perch with its hind legs, the hold being recovered by the hands. This became more marked after the fatigue due to escaping into a tree, where the animal climbed readily, but in letting itself fall was unable to catch the branches with its hind limbs. Both animals, when killed at 41 and 43 days respectively, were equally affected.

*Transmission of the Disease from Monkey to Monkey.*

Monkey 3 is interesting. It is a demonstration of the transmission of the disease from monkey to monkey, and moreover illustrates a long duration of the disease, viz. 30 weeks. After developing the usual symptoms at 5-6 weeks it apparently recovered. It had a relapse after about three months from which it appeared to recover imperfectly. General muscular weakness without any evident paralysis persisted. The monkey gradually went downhill, and at the end of six months was very weak and ill. Its condition outwardly appeared like another monkey (No. 4) which had not been inoculated, but was killed, because it was in very bad health and found to be suffering from tuberculosis. A considerable amount of blood was noticed about the mouth at times of Monkey 3 some days before it was killed, and haemoptysis was suspected. At autopsy it was found that the tip of the tongue had been bitten off—possibly in some unnoticed convulsive seizure. The lungs and other organs showed no evidence of tuberculosis.

Monkey 2, as will be seen from Tables (1) and (2), was originally inoculated with emulsion of human cord. Its symptoms, as recorded above, had been relatively mild as compared with Monkey 1, so that it was judged to have recovered at 9½ weeks, and then reinoculated with emulsion from the cord of Monkey 1. The reinoculation was followed by no immediate symptoms. A month later, i. e. during January, when it was very cold, it developed a violent cough and appeared to be suffering from nasal catarrh, and generally not very well; nothing untoward was, however, anticipated when I went on leave on February 21, only instructions given to have it carefully watched and kept warm. By February 23 it was very ill, and vomited and died suddenly at 10 a.m. on February 24. In this instance one may be dealing with another case of the chronic course of the disease as in Monkey 3, and, therefore, not with the pure results of direct inoculation from monkey to monkey. On the other hand, the short interval before a fatal issue, 11 weeks as compared with 30 weeks in the former, rather suggests that the course of the disease had been accelerated by the reinoculation.

It will be observed that the onset of the disease in monkeys was, therefore, insidious; but although so gradual, it was, nevertheless, well developed in all of

the nine animals inoculated in from 5 to 6 weeks, and thereafter, in slight cases, recovery appeared to set in, so that some animals were killed. One was reinoculated with fatal result, and one still remains alive. In another case the disease persisted, and, as the histological findings showed, progressed during  $7\frac{1}{2}$  months.

#### *Pathological and Histological Examination.*

In the autopsies performed after killing with chloroform, there was as little to attract attention as in man. There was nothing quite at the site of inoculation. In the earlier cases there was some emaciation found to be due to healthy monkeys securing more than their share of food. In the later cases, where this was avoided, the animals were well nourished and with abundant subcutaneous and mesenteric fat. There might be a little congestion of the meninges, but it was inconstant. The only constant features were a considerable hyperplasia of all lymphatic glands and some congestion at the bases of the papillae of the kidneys. None of the monkeys exhibited evidence of intercurrent disease, such as tuberculosis.

#### *Histological Examination.*

As in the case of man, the large amount of material collected has been subjected only to partial examination as yet. It pertains to cases from 6 weeks to 30 weeks after inoculation.

*Nerves.* These presented similar features to those described for man, but the evidence of acute neuritis, with an inflammatory exudate and haemorrhages, was never found so marked as in Figs. 3 and 4.

Wallerian degeneration, on the other hand, was just as marked, and is illustrated again because of its interest for the phrenic nerves after staining by osmic acid and Marchi. Figs. 11 and 12 bring out the same features as those shown in Figs. 5 and 6 for man.

*Spinal cord.* In a monkey killed at  $8\frac{1}{2}$  weeks, the features agree in all essentials with those described for man, except that the proliferation of the ependymal cells of the neural canal of monkeys was never marked and sometimes absent altogether. Fig. 13 shows the general appearance of the cord from a human case for comparison with Fig. 14 from Monkey 1 inoculated from it, the cord being shown under somewhat higher magnification for the monkey. The absence of inflammatory exudate from the meninges and the ramifications of the pia mater, as well as from the vessels, is apparent. The minute and irregularly distributed haemorrhages are characteristic of both. The contrast in the number of the haemorrhages is a mere accident of the levels at which the two sections have been cut: at other levels this relationship was reversed. The enlarged perivascular spaces without cell-contents, except occasional haemorrhage, have been a constant feature of all the human and animal cases. Throughout the cord

there is a small diffuse round-celled infiltration, left out of Figs. 13 and 14 for clearness. This infiltration is most marked around some groups of nerve-cells, but, as in man in the earliest stages (as described for Case VI), the large motor cells of the anterior horn are relatively exempted as contrasted with the several groups of tract-cells (see Fig. 15). These groups of nerve-cells appear to be attacked not only earlier, but in most cases also more markedly than any others. Specimens of degenerating nerve-cells from the group shown under low power in Fig. 15 are given in Figs. 16 and 17. The cells have lost their natural outline in varying degree. Eccentricity of the nucleus and nucleolus, with or without loss of the staining power of the nuclear membrane, is shown in varying degree. In Fig. 16 a cell is shown with a very misshapen nucleus. The shrunken condition of the cells is evident in Figs. 16 and 17, as is the abnormal clumping or powdery state of the tigroid substance. One cell is seen to have lost all its processes. A similar cell is seen in Fig. 21. In others the dendritic processes are swollen as compared with the size of the cell itself, in yet others round cells are applied closely to the processes or to the cell body into which a bay has been pushed. The cells of the anterior horn do not escape entirely, and there fairly healthy cells may be encountered in close proximity with those which are much degenerated, as in Fig. 16, where a badly degenerated cell, with its cytoplasm and tigroid substance almost lost and surrounded by round cells, is seen in close proximity to an almost normal cell, as described for man, the latter showing only slight eccentricity of the nucleus, slight clumping of the tigroid substance, and one vacuole. The tigroid substance may disappear from the periphery, as in Fig. 17, or the nucleus and cytoplasm stain irregularly with haematoxylin or methylene blue and eosin, as in Figs. 16, 17, and 20.

In the two monkeys inoculated respectively with emulsion of cord and culture from the same source, and killed at 6 weeks, all the foregoing changes were present in less degree than at 8½ weeks. They were quite definite, but the relative exemption of the large cells of the anterior horn was striking when compared with the marked degeneration and round-celled infiltration in the vicinity of the tract-cells on either side of the commissure, the Golgi cells, and the cells of the postero-lateral tract (Figs. 18-21).

In the monkey killed after 30 weeks the involvement of the nerve-cells had become more general and the cells of the anterior horn were more involved. There was also a considerable diminution of the total number of nerve-cells, and in their place only groups of round cells apparently surrounding what little remained, if there was anything, of cells such as those shown in Figs. 16-21. The changes were more marked in the lumbar than in the cervical region, particularly so in this chronic case; nevertheless, this distinction held good in all cases. This monkey was of special interest, because in addition to more marked proliferation of the ependymal cells of the neural canal, so that they formed little prolongations in the commissure, the vessels were surrounded by a homogeneous (hyaline) substance such as is shown in Figs. 8 and 9 for Case III, and only found in this one case for man.

*Posterior root ganglia.* As in man, so in the monkey, only the cervical ganglia were specially preserved in the earlier cases and did not show much, if any, change. From the three later monkeys (3, 8, and 9) they were carefully dissected out, both from the cervical and lumbar regions. Slight changes only were observed in the cervical region, except in the chronic case (No. 3). In the lumbar region, however, the changes were more evident, but marked only in the chronic case. As shown in Fig. 22, there is a patchy round-celled infiltration between the cells, and some infiltration of the nerve-fibres, together with eccentricity of some of the nuclei. The infiltration, while resembling, does not amount to anything like the enormous infiltration described in acute anterior poliomyelitis. Fig. 23 shows a group of cells from the periphery towards the centre of the ganglion depicted in Fig. 22. There is a fairly normal cell at the top left-hand side, and another below it to the right; all, however, show some irregularity in the grouping of the tigroid substance. To the right of the top of the figure there is a cell showing irregularity in the distribution of its cellular coating, with marked disappearance of the tigroid substance, especially at one side, and below and to the left of it the cellular coating of another cell has separated from the cytoplasm and shows a too numerous and too irregular distribution of the nuclei of its cellular coating, together with slight eccentricity of the nucleus of the nerve-cell itself. This eccentricity of the nucleus of the nerve-cell, as of the other features just mentioned, is seen in more marked degree in various other cells. One cell shows a marked vacuole. Between the nerve-cells there is a distinct infiltration of small round cells which are not distinguishable readily if at all, from those forming their cellular wall; indeed, it almost looks as if they had proliferated and provided the infiltration in places. This remains, however, a moot point. No haemorrhages were seen. It was curious to note that while the round-celled infiltration in the cord had subsided and persisted only around the remains of degenerated nerve-cells, in the ganglia it appeared still active. The types of cells appear, however, to be different in the two situations. Another interesting point is the marked infiltration of the ganglia of the lumbar enlargement as compared with the cervical.

*The motor cortex, cerebellum, and pons* showed the same features as in the human cases, but only marked for the monkey with the most prolonged duration.

The oedema of the face in Monkey 1 had suggested the examination of the kidneys. In all cases there was a patchy glomerular and tubular nephritis, except for the chronic case, in which the examination has not yet been made. The liver showed in all cases the small round-celled infiltration of the portal tract described for man.

The voluntary muscles showed the same features of fatty degeneration, and in the case of the monkey which died suddenly there was a similar slight degeneration of the diaphragm revealed by osmic acid. It has not been possible to carry out staining with Marchi.

*Microscopical Examination of the Cord of Man and Monkeys for  
Evidence of Organisms.*

So soon as the infective nature of the disease had been demonstrated by the transmission of the disease from man to monkey and monkey to monkey, material for bacteriological examination was passed on to Capt. Wilson. Thereafter a careful search of sections of cord and posterior root ganglia was made for the presence of organisms, after staining by Gram, by methylene blue and eosin, Giemsa, Leishman, &c. In the spaces around the degenerated nerve-cells both in man (Case II) and in the monkey inoculated from it, very minute bodies like diplococci enclosed in a capsule were seen, and they were also encountered in the posterior root ganglia, especially where a nerve-cell had shrunk away, as it were, from its cellular capsule. In one case these bodies were encountered in a definite group, as if embedded in a structureless mass, lying amidst a small-celled infiltration between the nerve-cells of the ganglion. Capt. Wilson and myself were in agreement that these diplococcal-like bodies were suggestive of some definite organism, but their minute size and the liabilities to error, owing to the numerous minute fibrils cut crosswise, together with the great eye-strain associated with the prolonged looking for and at them, led to this line of investigation not being pursued. It was rendered unnecessary by the results attending Capt. Wilson's cultures.

*General Conclusion.*

The clinical and pathological features of the disease have been reproduced in monkeys by the subdural inoculation of the emulsion of human cord preserved from 25 days to 7 months in glycerin, and also by direct inoculation from monkey to monkey of emulsion of the fresh cord or of cord preserved in glycerin, and, moreover, by the inoculation of the pure culture prepared by Capt. J. A. Wilson. The disease has not yet developed after the lapse of six weeks since the inoculation of the filtrate obtained from Capt. Wilson's culture. These facts, together with the apparently definite incubation period of from 5 to 6 weeks, lead to the conclusion that we are dealing with a specific infective disease of a gradually ascending nature from the nerves to the entire central nervous system. Pathologically, it appears to be distinguishable from acute anterior poliomyelitis, although closely allied to it, and suggesting that this term and those applied to other hitherto obscure diseases of the nervous system (Landry's paralysis, acute ascending paralysis, polioencephalitis, and yet others) may ultimately be found to cover or be overlapping designations for a group of closely allied and infective diseases of the central nervous system. Perhaps, indeed, a new impetus has been given to the investigation of much that still remains obscure in the diseases of the nervous system as a whole.

The investigation is obviously still incomplete, both histologically and



experimentally, but it is hoped to fill in some of the more glaring lacunae as the conditions of active service permit.

It would not have been possible to carry this investigation to its present successful conclusion without the indispensable assistance of Major Guise, B.R.C.S., and Capt. Abrahams, B.R.C.S. I desire also to record the valuable services rendered by Corp. T. C. Reynolds, R.A.M.C., and Pte. D. N. Vidgen, R.A.M.C.

In conclusion, I have again to express my indebtedness to the Trustees of the Beit Memorial Fellowship Fund for defraying all the expenses connected with the investigation.

#### REFERENCE.

1. Holmes, Gordon, *Brit. Med. Journ.*, 1917, ii. 37.

### PART III

#### THE ISOLATION AND CULTURE OF THE VIRUS OF THE DISEASE

By J. A. WILSON

##### 1. *Introduction.*

The successful transmission by Flexner and Lewis (1) of the virus of anterior poliomyelitis from fatal human cases to monkeys was the first actual proof of the essentially infective character of the disease, and further, was the foundation of a series of investigations, cultural and immunological, on the nature and properties of the infecting agent. The most significant result of the investigations was the discovery of 'the globoid bodies' by Flexner and Noguchi (2)—minute, rounded or oval, non-motile organisms 0.15 to 0.3  $\mu$  in diameter—in the nervous tissues of fatal cases of the disease. Applying the principles introduced by Noguchi (3) for the cultivation of the spirochaete of syphilis, these observers not only grew the organism and studied its cultural and immunological characters, but, more important from the aetiological point of view, they inoculated monkeys, subdurally, with cultures of the organism, thereby reproducing the disease in its clinical and pathological features, and subsequently recovered the organism, post-mortem, from the lesions in the nervous tissues so produced. In this way the position of the globoid bodies, as the causal agents of anterior poliomyelitis, was established.

The place occupied by the globoid bodies in the biological scale has not, so far, been determined. Rosenow (4, 5) suggests that they are produced by the breaking down of a large coccus, and regards them as merely a stage in the development of the pleomorphic streptococcus described by him as the causal agent of the disease; they are 'the anaerobic and, according to Amoss's results, the non-antigenic form of the organism which, under aerobic conditions, clearly belongs



to the streptococcus group of organisms'. The fact that these streptococci do not reproduce the disease when experimentally inoculated 'is due to the development of anti-bodies, since the organism in the aerobic form has marked antigenic properties'. If the difference between the two organisms were along these lines, then a streptococcus of Rosenow's type, isolated by aerobic methods, should, when cultivated anaerobically and inoculated into monkeys, subdurally reproduce the disease. But such is not the case, and Rosenow cannot be considered to have proved his argument, so the identity of the globoid bodies remains unsolved.

The disease, the subject of this communication, having been transmitted to monkeys by Capt. Bashford, an attempt was made to grow the virus from the nervous tissues. The ordinary methods of culture, aerobic and anaerobic, failed to demonstrate organisms other than those which were obvious contaminations, and it was only when the technique of Flexner and Noguchi was employed that success was attained.

The materials used for cultural purposes were obtained from two fatal human cases, and from four monkeys inoculated with emulsions of spinal cord from fatal human cases, viz. Monkeys 1, 2, 3, and 9. An account will be given of the cultural and microscopical characters of the organism isolated from such materials, with a note on the probable relation of the organism isolated to the globoid bodies described by Flexner and Noguchi in cases of anterior poliomyelitis.

## 2. *Technique of Culture.*

Into each of a series of sterile test-tubes ( $6 \times \frac{3}{4}$ ") a fragment, about the size of a pea, of sterile guinea-pig kidney is placed, and alongside it a fragment, similar in size, of the nervous tissue, cerebral cortex, or spinal cord from the suspected case. Serum agar, in the proportion of one part of inactivated guinea-pig or horse serum to ten parts of melted nutrient agar at a temperature of about  $48^{\circ}\text{C}$ ., is added to each tube in an amount just sufficient to cover the tissues. After solidification of the serum agar has taken place there are added to each tube fifteen cubic centimetres of serum bouillon—one part of inactivated serum, as in the case of the agar, to ten parts of bouillon at a temperature of  $45^{\circ}\text{C}$ .—and complete anaerobiasis obtained by running on the surface of the medium sterile liquid vaseline, at a similar temperature, and to a depth of at least half an inch. The completed medium, therefore, consists of a thin layer of serum agar, containing fragments of sterile guinea-pig kidney and suspected nervous tissue, with a superimposed column of serum broth, the whole being sealed with a moderately thick layer of vaseline.

Apparently quite a simple process, yet in actual practice there are several technical difficulties. It will be observed that, in the making of the medium, there are five stages which involve the opening of the test-tubes, and at each there is a risk of contamination; hence the necessity for a series of culture tubes.

The guinea-pig kidney is another fruitful source of trouble. Quite apart from the risk of contamination in the removal of the organs, it not infrequently happens that they, though presenting no gross evidence of disease, are infected with *B. pseudo-tuberculosis rodentium*. Much useless labour may be avoided if, before using the organs, a careful examination is made of the liver, small intestine, and mesenteric glands. The occurrence of small yellowish-white nodules on the surface of the liver, or in sections of it, of the slightest congestion of the small intestine, of enlargement or congestion of the mesenteric glands, should condemn the kidneys for cultural purposes.

The nervous tissues from fatal cases of the disease are, as a general rule, grossly contaminated, and it becomes necessary to take advantage of the resistance to glycerin of the specific organism. The tissues should be immersed in 50 per cent. glycerin and examined from day to day for evidences of aerobic and anaerobic contaminating organisms. The time required in this process is from seven to ten days.

Another point of importance is the use of inactivated sera in the preparation of the serum agar and serum bouillon. Fresh serum was found to exert an inhibitory effect on the growth of the organism, if not actually prevent it in some cases. It follows, therefore, that the guinea-pig whose kidneys are to be employed in the making of the medium should be bled as thoroughly as possible.

Lastly, a series of controls, involving the various elements employed in the medium, must be put up.

### 3. *Characters of the Culture.*

The medium remains unchanged until the fourth or fifth day, when a faint granular haze is observed in the serum agar in the vicinity of the nervous tissue. The haze gradually deepens, at the same time extending throughout the serum agar. About the seventh day minute semi-translucent colonies may be seen on the surface of the agar, and from this stage onward growth is rapid. The surface colonies increase in size, assume a faint yellow colour, and their upper limits become irregular. By the twelfth to fourteenth day the colonies have united to form a yellow-brown continuous layer, showing slight elevations on its surface, while the serum agar has become definitely opaque. About this time evidence of growth may be observed in the lower portions of the serum bouillon, but unless the surface agar growth has been disturbed it is not a marked feature. Towards the end of the third week the serum agar has become dense, a faint pink tint being imparted to it by the autolysis of the kidney tissue. A slight increase in thickness of the surface growth is to be noted, associated with an accentuation of the corrugations. If the culture tube, at this stage, is rotated vigorously between the palms of the hands, the layer of growth breaks up into irregular masses, which seem to be possessed of considerable cohesive powers and resist further efforts to subdivide them. The subsequent changes

occur principally in the serum bouillon, which becomes opaque and finally turbid.

The substitution of ascitic fluid or serum water for the serum bouillon is not attended by any appreciable change in the quality or quantity of the growth.

The same features are developed in subcultures, but it is a noteworthy fact that the growth becomes more scanty in successive generations. Growth does not pass beyond the isolated colony stage in the fourth generation of a strain, and no strain has been carried beyond the fifth generation. It would appear that it is an organism possessed of feeble saprophytic powers.

The conditions of growth, whether a primary culture or subculture is in question, are of a strictly limited character, and remain so. All attempts to grow the organism aerobically have failed; it is an anaerobe. Furthermore, it will only grow under the selected conditions detailed above. No growth occurs in the absence of the animal tissue or in the presence of the animal tissue, the serum constituents of the agar and bouillon being absent.

Incubation must be carried out at 37° C., no growth occurring at room temperature. The resistance of the organism to heat is not great. It withstands a temperature of 45° C. for fifteen minutes, but exposure for a similar period to 60° C. proves lethal.

#### 4. *Morphology and Staining Reactions of the Organism.*

In suitably stained film preparations from cultures five to ten days old, the organism appears as a minute, rounded, oval, or kidney-shaped body, measuring 0.2 to 0.5  $\mu$  in diameter. It presents a darkly-stained, rounded spot, eccentrically placed, which is surrounded by a narrow faintly-stained area. The organisms are grouped in colonies, and it is sometimes difficult to determine the limits of the individual elements, so that the colony conveys the impression of a multinucleated plasmodium. More usually, however, the individual elements can be distinguished, when it is found that they are arranged in pairs, or in irregular small groups of five to eight organisms, or, and more rarely, in short chains of three to five. As the cultures become older the organisms swell up, lose their selective staining, and become indefinite in outline. The plasmodial appearance is in this way intensified, a few darkly-stained bodies being seen in a relatively large faintly-stained mass.

By the overlapping and flattening of the coccal elements in a colony, bacillary forms are not infrequently produced. These bacillary forms are most varied, sometimes short and spindle-shaped, like a miniature Hofmann's bacillus, sometimes longer, more slender, curved, giving a barred appearance; but, if careful examination is made, the true nature of such forms can be established.

The preparation of adequately stained films presents some difficulty. The ordinary dilute solutions of aniline dyes have but little effect on the organism, and it is necessary to make use of a mordant, such as tannic or carboic acid. After treatment with a mordant the film may be stained with Loeffler's or poly-

chrome blue for twenty minutes. Giemsa's stain, even when applied for two hours at 37° C., does not give a satisfactory result unless the film has been previously mordanted. Young cultures retain the stain in Gram's method, but after the second week the preparations are, as a rule, decolorized. Gram's stain does not bring out the differentiation noted with Loeffler's and polychrome blue. The organism is not acid-fast.

By dark-ground illumination it is merely a minute, highly-refractile, and undifferentiated body.

##### 5. *Relation of the Organism to the Disease.*

An organism of definite microscopical and cultural characters has been isolated from the nervous tissues of two fatal cases of polyneuritis, and also from four monkeys inoculated with emulsions of the spinal cord from three such cases. The cultivated organism, inoculated subdurally into a monkey, has reproduced the disease clinically and pathologically, and finally the organism has been recovered, post mortem, from the nervous tissues of the animal so inoculated. This organism is considered, therefore, to be the cause of polyneuritis.

The distribution of the organism in the nervous system would seem to be wide. It has rarely happened that a culture has failed to give a growth of the specific organism, unless in those instances where contamination of the medium had taken place. Of special interest, in view of the absence of related symptoms, has been the recovery of the organism with comparative ease from the cerebral cortex. In the monkey, though not in a human case, the organism has been recovered from the cervical lymphatic glands.

##### 6. *Relation of the Organism to the Globoid Bodies of Poliomyelitis.*

The discussion of a relationship between the two organisms, as far as their morphological and cultural characters are concerned, is discounted at the outset by the fact that it has not been possible to obtain material, for cultural purposes, from cases of anterior poliomyelitis. In default of this standard there remains the unsatisfactory procedure of comparing the polyneuritis organism with the published descriptions and plates of American authorities on the globoid bodies.

Taking the subjects of morphology and staining reactions first, the two organisms show a similarity which is most striking. They are both very minute, rounded or oval, non-motile organisms which, when stained by suitable methods, show a characteristic differentiation into a deeply-stained eccentrically placed portion and a narrow faintly-stained margin. They show the same occasional formation of streptococcal and bacillary forms, and in their involution they follow the same course. But there is a distinction—it may be that it is purely a question of technique—namely, that the polyneuritis organism is more definite in its characters, inasmuch as these are constant at a given period and for a given medium. Amoss (6) and Smillie (7), two of the most recent writers on

the globoid bodies, lay stress on their variability in morphology and staining reactions.

With regard to their actual features, the two organisms are in general agreement. They both show certain limitations as regards choice of medium and temperature of incubation. The presence of animal tissue is necessary in the first, the temperature must be that of the body in the second. They are strict anaerobes. The course of the growth under such conditions appears to be identical. The only difference determined is that all authorities are agreed on the fact that the globoid bodies become more and more saprophytic in subcultures, while the reverse is the case in the cultivation of the polyneuritis organism; it becomes increasingly difficult to grow in subcultures, and, as noted above, usually dies out in the fifth generation.

Perhaps of little significance, still a point of distinction is to be found in the distribution of the two organisms in their respective diseases. Smillie (loc. cit.) alludes to the number of 'no growths' in his cultures from the nervous tissues of cases of poliomyelitis; such is not the case in polyneuritis, the organism apparently having a very wide distribution.

On the question of pathogenesis the discussion is on a much more sound basis, for, in this respect, the difference between the two organisms is of the most significant kind. The organism isolated from cases of polyneuritis inoculated subdurally into monkeys produces a disease which is clinically and pathologically distinct from anterior poliomyelitis, a disease which is identical with that from which it was obtained.

From a consideration of the above facts, it is suggested that the two organisms, while having a group relationship, are nevertheless distinct entities.

#### 7. *Biological Position of the Organism.*

The problem of the position of the globoid bodies is also the problem of the organism of polyneuritis. A certain amount of evidence is available that the organism whose characters have been described is the involution form of a still more minute coccus. It is hoped, by a series of filtration and inoculation experiments, to definitely determine the point.

In conclusion the writer would like to acknowledge the help of Capt. Bashford, R.A.M.C., who has carried out the inoculation experiments, and of Sergt. G. K. Maxwell, R.A.M.C., whose reproductions so adequately bring out the characters of the cultures and films.



## REFERENCES.

1. Flexner and Lewis, *Journ. Amer. Med. Assoc.*, 1909, liii. 1639.
2. Flexner and Noguchi, *Journ. Exper. Med.*, New York, 1913, xviii. 461.
3. Noguchi, *ibid.*, 1911, xiv. 99.
4. Rosenow and Towne, *Journ. Med. Res.*, Boston, 1917, xxxvi. 175.
5. Rosenow and Wheeler, *Journ. Infect. Dis.*, Chicago, 1918, xxii. 281.
6. Amoss, *Journ. Exper. Med.*, New York, 1917, xxv. 545.
7. Smillie, *ibid.*, 1918, xxvii. 318.

## DESCRIPTION OF ILLUSTRATIONS.

PLATE 1. Series of culture tubes showing the characters of the growth at different periods of incubation:

- |              |              |              |
|--------------|--------------|--------------|
| (a) Control. | (c) 14 days. | (e) 28 days. |
| (b) 10 days. | (d) 21 days. | (f) 6 weeks. |

Oblique view of surface growth at

- |              |              |
|--------------|--------------|
| (g) 10 days. | (h) 28 days. |
|--------------|--------------|

PLATE 2. Microscopic preparations of cultures at three periods of incubation:

- (a) 10 days.
- (b) 14 days—showing streptococcal and bacillary forms.
- (c) 28 days—showing the involution changes.

PLATE 3, FIGS. 1 (Cervical enlargement) and 2 (Lumbar enlargement). To show irregular distribution of the lesions of the nerve-cells and their diffuse character. The intensity of the lesions is greater in the left anterior horn than in the right in the cervical enlargement, the reverse obtaining for the cells in the posterior root. In the lumbar enlargement the whole of the grey matter of the left side of the cord is more affected than the right. Note the swelling of the grey matter of the left half of the cord in the cervical enlargement (monkey).

FIGS. 3 and 4. Acute neuritis (man, Case II). Two sections from a series of the sciatic nerve to show increase in cells of Schwann; an inflammatory exudate with round cells and haemorrhages between nerve-fibres.

PLATE 4, FIGS. 5 and 6. Phrenic nerve (man, Case V) stained respectively with osmic acid and by Marchi's method to show the greater amount of degeneration revealed by the former (Fig. 5). Note swelling and loss of motal arrangement of sheath with granules of degeneration or irregular rings. Swelling and disintegration of axis cylinders. Non-medullated fibres relatively exempt.

FIG. 7. Group of degenerated nerve-cells (man, Case II). Note absence of round-celled infiltration around two capillaries. Eccentricity of nuclei of nerve-cells. Clumping and powdery arrangement of the tigroid substance. In bottom left-hand corner a cell with excess of fat-like pigment, and in bottom right-hand corner cell which has lost all its processes.

PLATE 5, FIGS. 8 and 9. Proliferation of ependymal cells of neural canal (man, Case III) with a curious homogeneous (hyaline) degeneration surrounding the vessels, better seen under higher magnification in Fig. 9, where it is also seen to affect some of the proliferated ependymal cells.

PLATE 6. FIG. 10. Fatty degeneration of voluntary muscle of leg (man, Case II). Note varied degree of incidence, adjacent fibres escaping altogether.

FIGS. 11 and 12. Phrenic nerve (Monkey 1) stained respectively with osmic acid (Fig. 11) and by Marchi's method. Note agreement with Figs. 5 and 6 from man, in the relative exemption or escape of some fibres as compared with others.



PLATE 7, FIG. 13. Cord (man, Case II) showing absence of infiltration of meninges, divisions of pia mater by round cells as in acute anterior poliomyelitis, and also absence of such cells from around the vessels. Irregular petechial haemorrhages. Proliferation of ependymal cells of neural canal. Large perivascular spaces. The diffuse small-celled infiltration has been omitted for clearness.

FIG. 14. Cord (Monkey 1) showing same features under higher magnification as Fig. 13. The more extensive haemorrhages and engorgement of vessels are an accident of the level at which section was cut. Note enlarged perivascular spaces free from round cells, but in one case containing red blood corpuscles.

PLATE 8, FIG. 15. Cord (Monkey 1) showing a group of degenerated tract-cells contiguous to healthy cells; diffuse round-celled infiltration not shown to its full extent for sake of clearness; accumulation of round cells around nerve-cells, but not around vessels. Dilated perivascular spaces, one containing red blood corpuscles. Slight proliferation of ependymal cells of neural canal.

FIG. 16. (Monkey 1.) Much-degenerated nerve-cell in proximity to a fairly healthy cell, which however contains a vacuole; shows some eccentricity of its nucleus and abnormal clumping of its tigroid substance. Advanced degeneration of an adjacent nerve-cell which is surrounded by round cells and a large space.

FIG. 17. Two cells in advanced degeneration. One has lost its processes and much of its cell body and is surrounded by round cells (neuronophagia). A second retains its processes to some extent, but nucleus, cytoplasm, and processes have lost their differential staining and retain eosin and methylene blue irregularly. A third shows loss of tigroid substance, most marked at periphery.

FIG. 18, and PLATE 9, FIGS. 19-21. (Monkey 1.) High-power view of group of degenerating nerve-cells shown in Fig. 15. Fig. 18: eccentricity of nucleus and nucleolus with loss of nuclear membrane. Tigroid substance well retained. Fig. 19: eccentricity of nucleus with a powdery condition of tigroid substance. Fig. 20: various cells in advanced degeneration, one with neuronophagia. Figs. 18, 19, and 20 show round-celled infiltration; Fig. 21 shows its absence around a capillary adjacent to a nerve-cell with eccentric nucleus and powdery tigroid substance.

FIG. 22. Post root ganglion of lumbar enlargement (Monkey 3). Note patchy round-celled infiltration between nerve-cells, also between nerve-fibres entering ganglion. Some eccentricity of nuclei of nerve-cells.

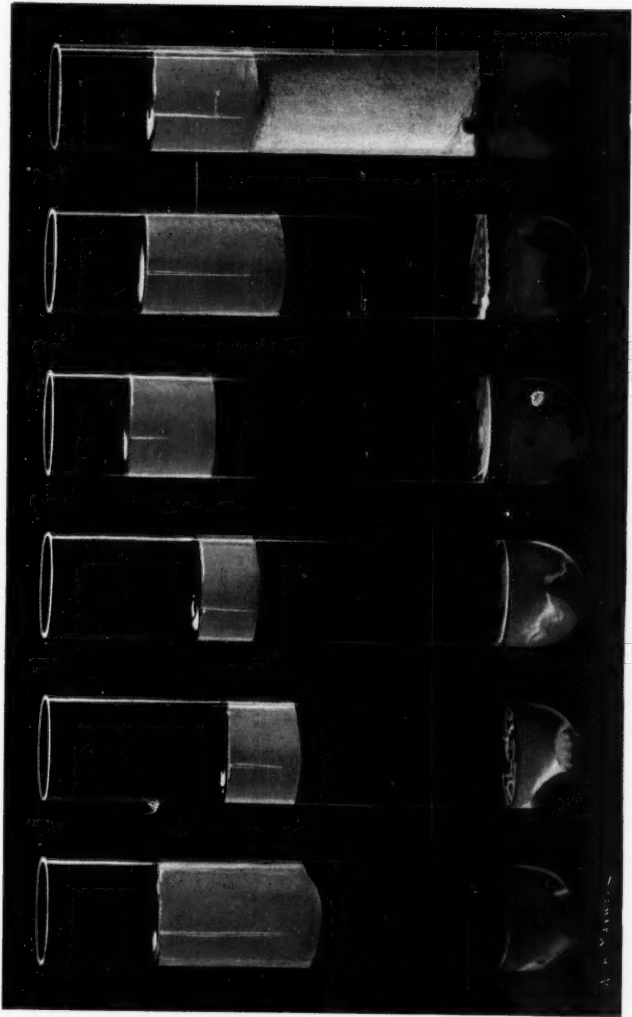
FIG. 23. Post root ganglion (Monkey 3). High-power view of group of cells from top of Fig. 23, passing inwards from capsule. Note fairly normal cell at top and to the left, others showing various stages in proliferation (?) of the cellular walls and eccentricity of nuclei. Various stages in loss of tigroid substance, one cell with a vacuole. Inter-cellular round-celled infiltration.



g



h



f

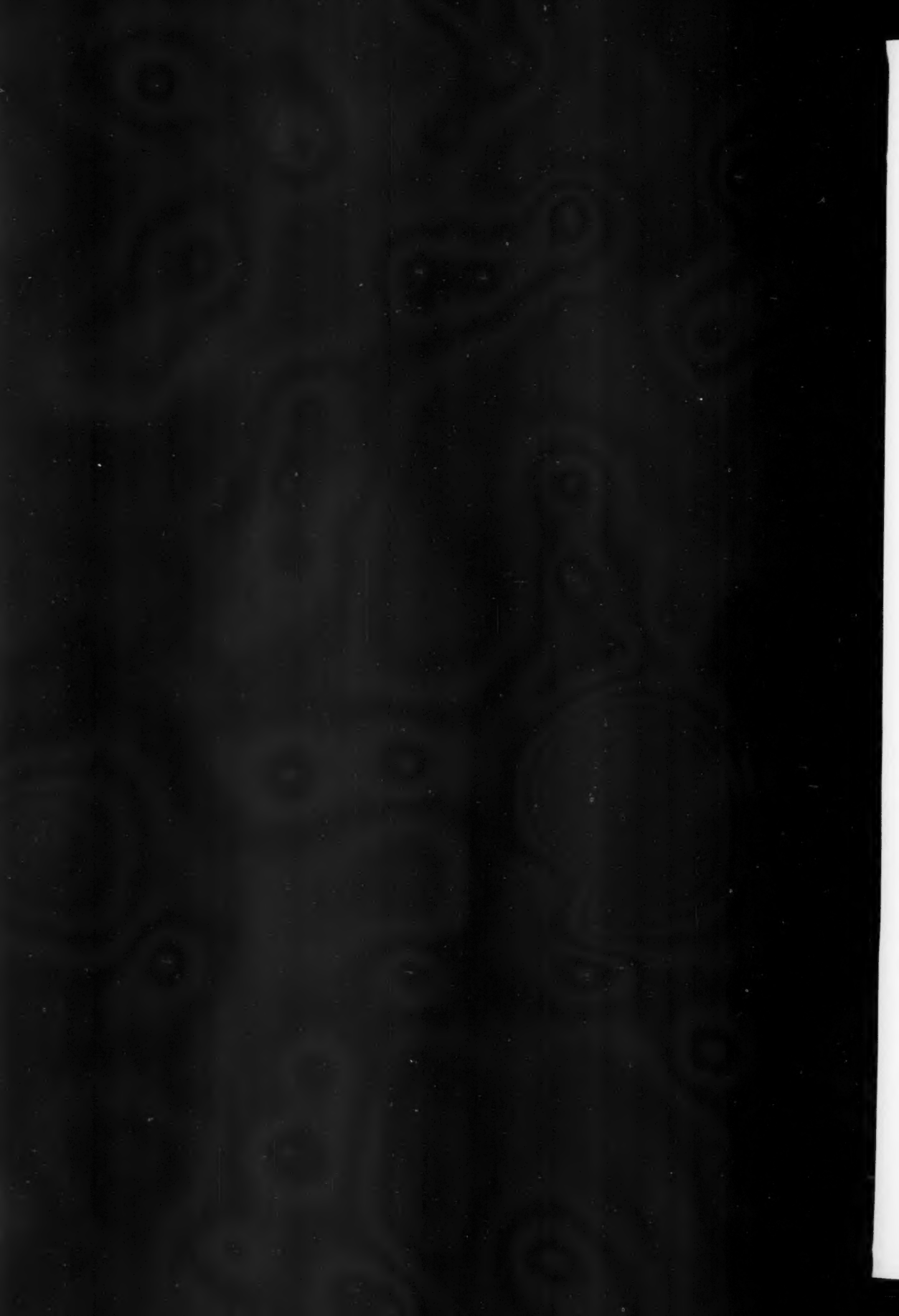
e

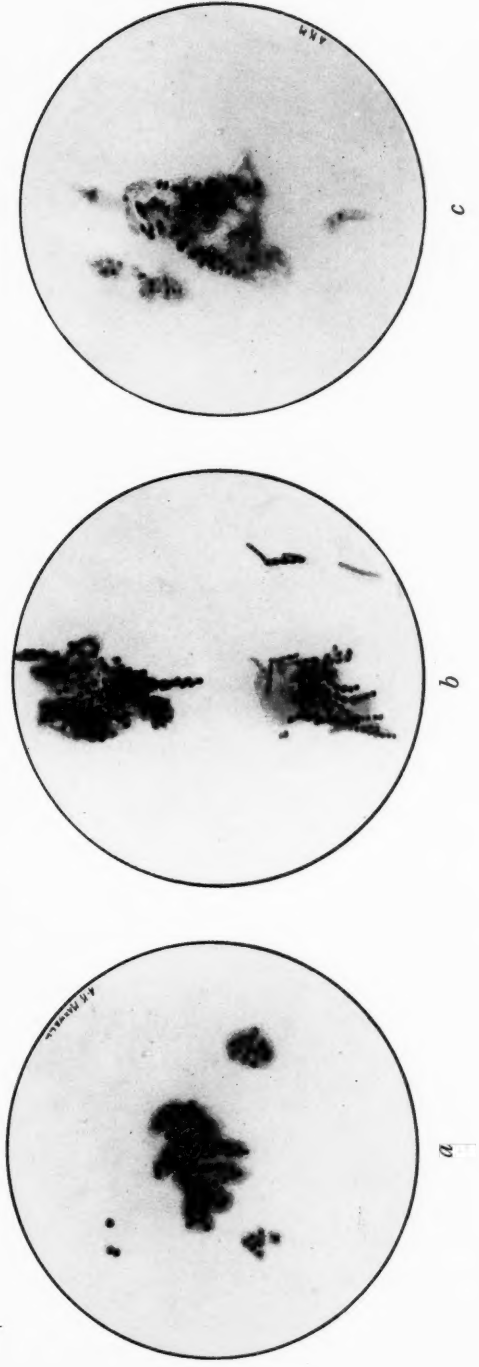
d

c

b

a







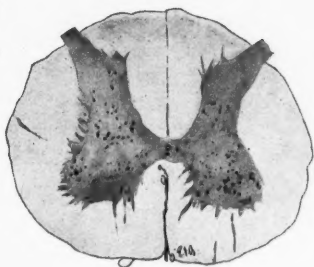


FIG. 1

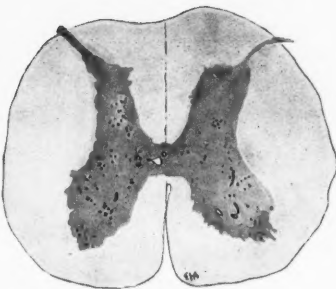


FIG. 2

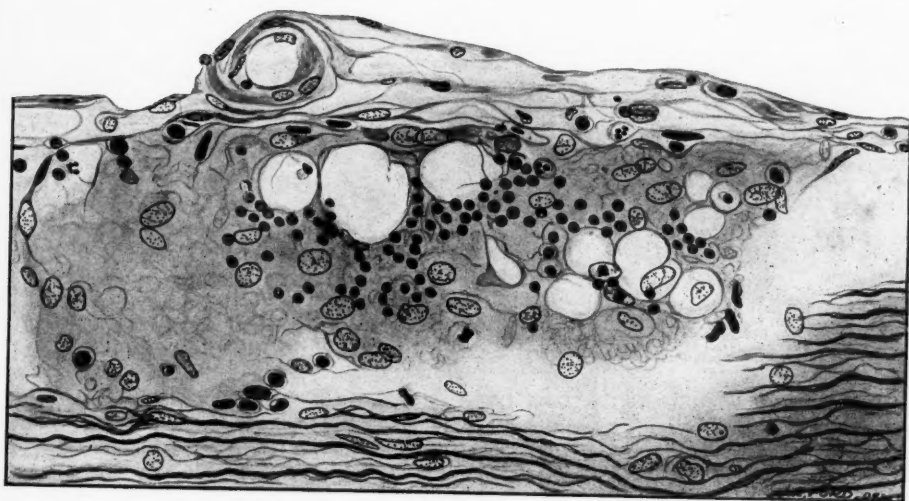


FIG. 3

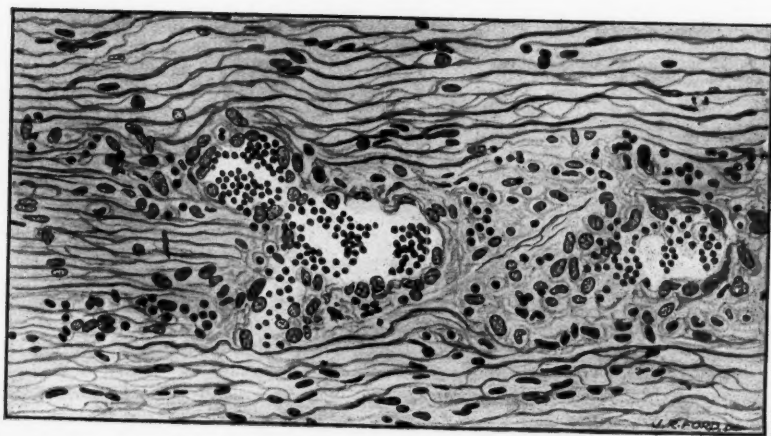


FIG. 4





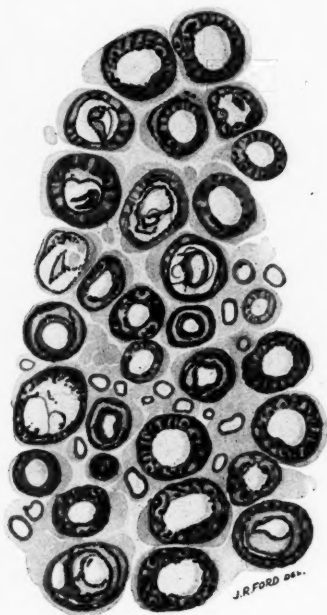


FIG. 5

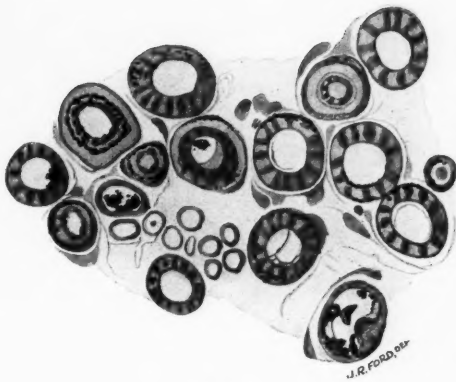


FIG. 6

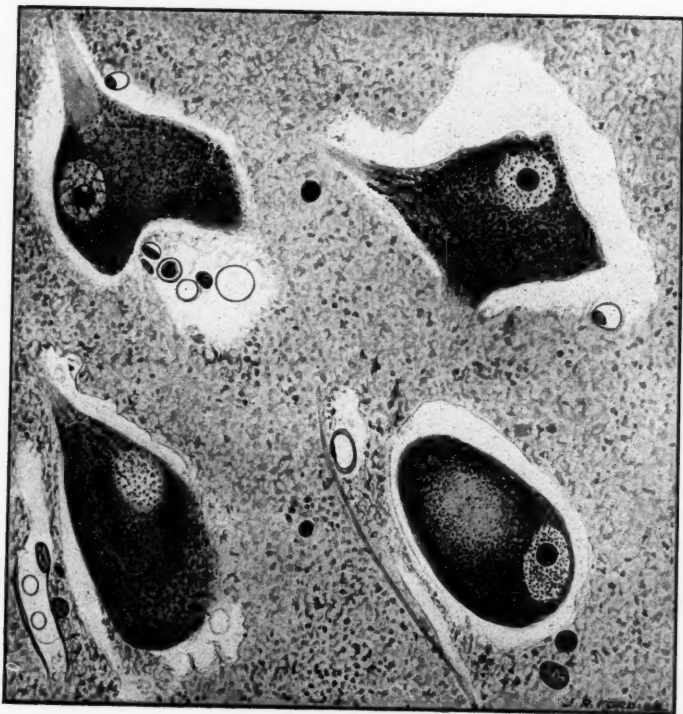


FIG. 7



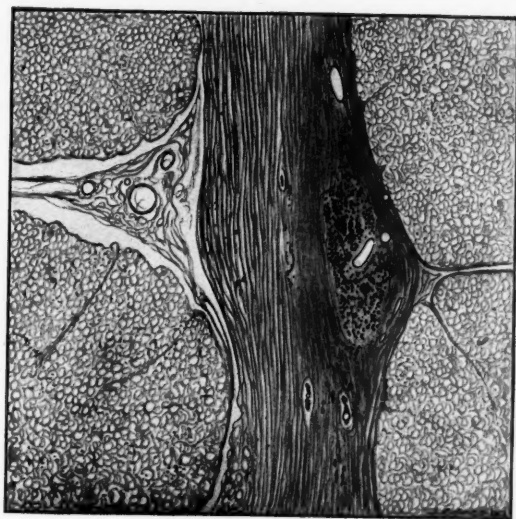


FIG. 8

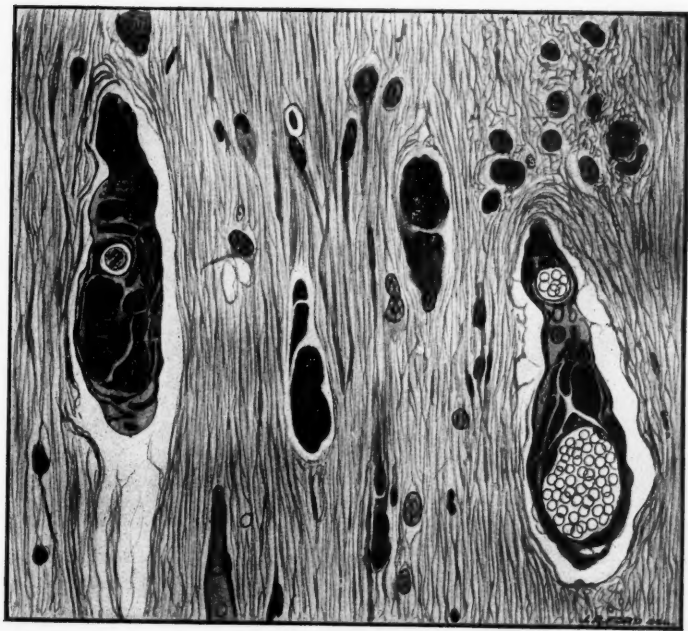


FIG. 9



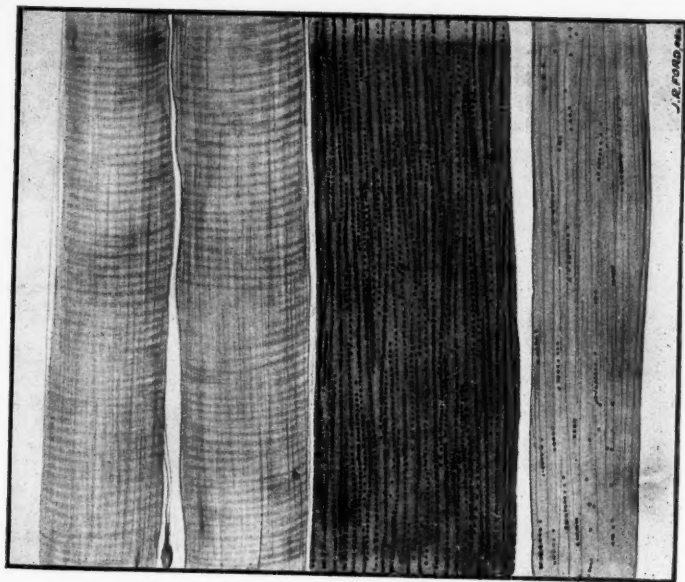


FIG. 10

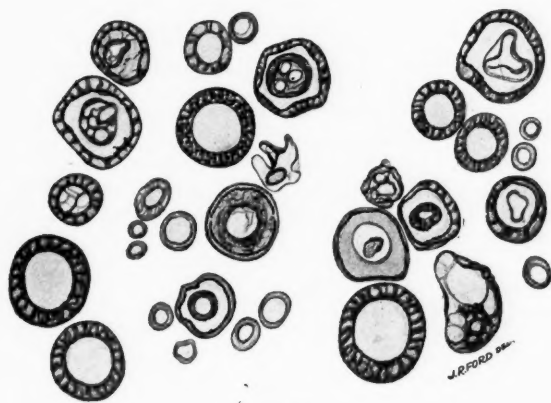


FIG. 11



FIG. 12





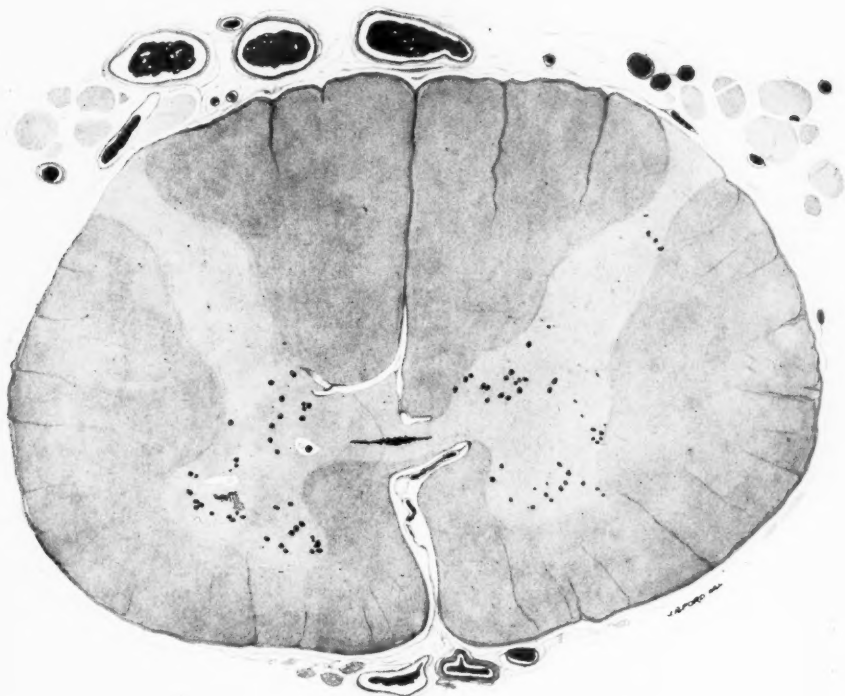


FIG. 13.

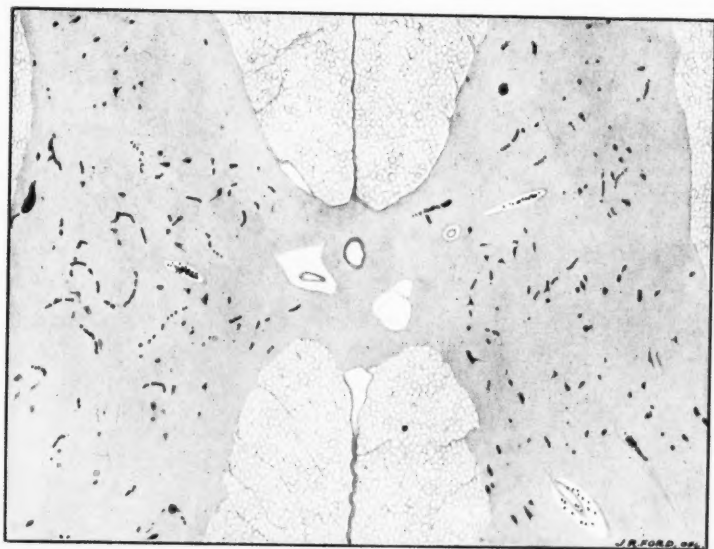


FIG. 14.





FIG. 15

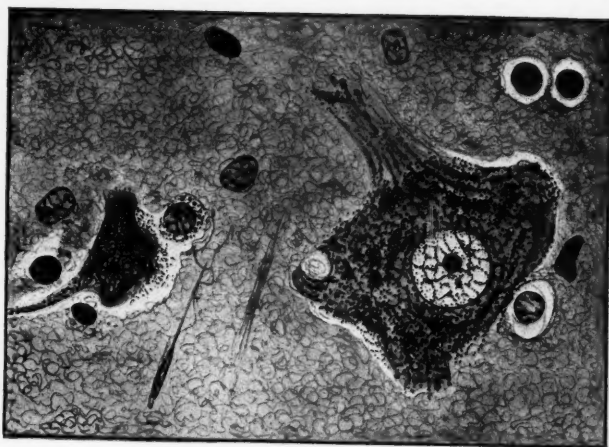


FIG. 16

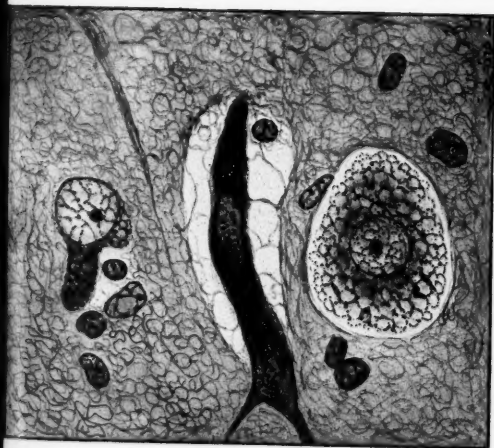


FIG. 17

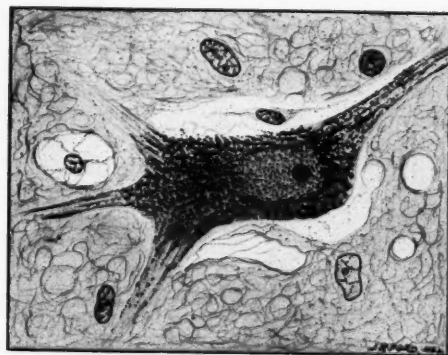


FIG. 18



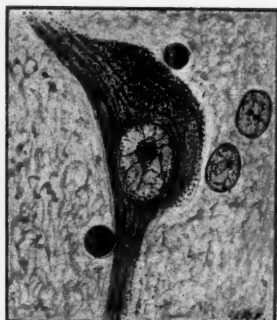


FIG. 19



FIG. 21

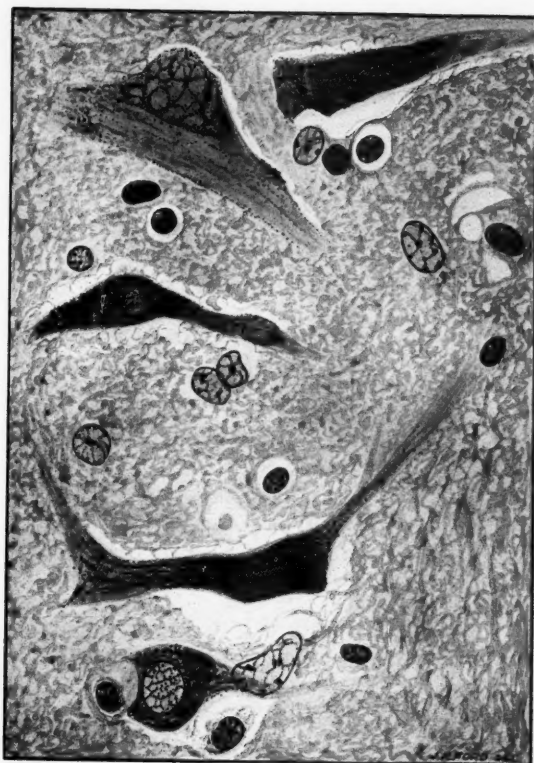


FIG. 20



FIG. 22

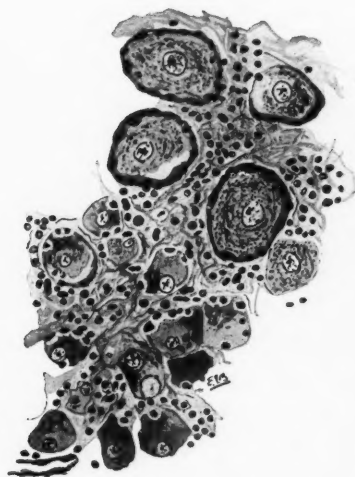


FIG. 23





# MASSIVE COLLAPSE OF THE LUNG AS A RESULT OF GUNSHOT WOUNDS, WITH ESPECIAL REFERENCE TO WOUNDS OF THE CHEST

By JOHN ROSE BRADFORD

With Plates 10-12

## I. *Introduction.*

THE study of the physical signs present in the chest in cases of gunshot wounds involving the chest-wall or its contents has been a subject of great interest during the present campaign, owing to the variety, complexity, and difficulty of satisfactory interpretation of the signs observed in many cases. On *a priori* grounds, it might be thought, inasmuch as the more common effect of such injuries is to cause either a collection of bloody fluid or a mixture of such fluid with air or gas in the pleural cavity, that the physical signs would be merely those generally regarded as characteristic of the presence of fluid or gas or both in the pleural cavity. A very slight experience of chest wounds, even when the lesion produced is a simple, sterile haemothorax, shows that this is far from the truth, and that in a very large number of cases, perhaps even in all, the signs are really different to those hitherto regarded as characteristic of the presence of fluid or gas in the pleura. Some observers have sought to explain the discrepancies by the suggestion that the lesions often present in the lung as the direct result of the laceration, &c., produced by the missile are the cause of the complexity and diversity of the signs present. Doubtless there is much truth in this view, but the object of the present paper is to draw attention more especially to another and relatively little-known condition, i. e. massive collapse of the lung, as a most important factor in the production of the clinical phenomena seen in cases of gunshot injuries of the chest. In the opinion of the writer, this is not only a most characteristic but also a common result in cases of gunshot wounds of the chest. It was not fully recognized until after a very extensive experience of chest cases, although it is, in all probability, really of frequent occurrence. It may be of interest to record shortly the stages in the process of its recognition.

1. The diaphragm in cases of simple sterile haemothorax was found, on clinical examination, to be abnormally high. This fact is most readily demon-

[Q. J. M., Oct., 1918, and Jan., 1919.]

strated in cases of left-sided haemothorax, since it is then easy to detect the upward displacement of the stomach and colon by ordinary percussion. X-ray examination not only confirmed the view that the diaphragm was displaced, but also showed that it was immobile on the injured side.

2. More extended experience and more careful observation showed that in many cases of haemothorax, and especially in cases of sterile haemothorax, the affected side of the chest was not only immobile, but the chest-wall was actually retracted, notwithstanding the presence of a considerable quantity of fluid in the pleural cavity. In some of these cases displacement of the heart towards the opposite or uninjured side was also present. Retraction of the chest-wall, notwithstanding the presence of fluid in the pleural cavity, is a common phenomenon in haemothorax; it is not always accompanied by this displacement of the heart, but when this is the case the clinical picture is a very remarkable one, and strikingly different to that associated with the mere presence of fluid, e.g. pleural effusion, in the chest. It is, of course, well known that in certain chronic pleural effusions, where the lung has been long compressed and has undergone secondary changes, such a condition may exist; but in haemothorax this clinical picture is not only an early one, but quite often is transitory, the retraction of the chest-wall disappearing and being perhaps replaced by bulging. This is especially seen in cases where the haemothorax is infected and there is a rapid increase in the amount of pleural exudate.

3. A small number of cases showed physical signs indicative of the presence of collapse, involving the whole of the lung on the side of the haemothorax, although the haemothorax was quite small in amount, in fact often so small as not to require special treatment. Such cases might, for instance, show dullness on percussion up to the clavicle, and yet the amount of fluid in the chest was not more than a few ounces; in other words, the degree of collapse was quite out of proportion to the size of the haemothorax.

4. At this stage in the study of haemothorax, the fact that the collapse of the lung should not necessarily be regarded as solely due to the bloody effusion was being slowly appreciated, and then a series of cases was observed where massive collapse involving the entire lung occurred on the side opposite to that wounded, and not only as a result of unilateral wounds limited to the chest-wall, but often of wounds slight or even trivial in character.

5. The recognition of massive contralateral collapse as a result of contour wounds led to the detection of less extensive areas of collapse as one of the contralateral complications of haemothorax, whereas previously cases presenting similar physical signs had been regarded as probably pneumonic in character. Although pneumonia may occur as a contralateral complication of haemothorax, especially in infected cases, yet many cases regarded as pneumonic are really not so, and the complication present is collapse and not pneumonic consolidation. The fact that contralateral massive collapse may occur as a result of a non-penetrating wound of the thoracic parietes, and the occurrence of homolateral massive collapse, involving the entire lung, in cases of slight haemothorax, raises

the question whether the collapse present in ordinary haemothorax is always due solely to the effusion, or whether it is not really an associated phenomenon of independent and different origin. If the collapse of the lung associated with haemothorax is not solely dependent upon the mere presence of the effused blood in the pleura, but is really produced in some other way, this might serve to explain the discrepancies between the clinical phenomenon as seen in cases of haemothorax and those present in pleural effusion. It seems obvious to regard the ordinary collapse of the lung in haemothorax as due to the mere effusion of blood, but if this really be the case, it is very difficult to understand why the clinical phenomena are so often different to those of other forms of pleural effusion. The raised position of the diaphragm, with the accompanying increase in the resonant area known as Traube's space, in haemothorax, instead of the replacement of this resonant area by dullness, as in pleural effusion, is more especially difficult to explain. At first the view was entertained that this difference might be due to the following considerations. The gunshot wound of the chest might cause the entry of air into the pleural cavity and so lead, even in a case of simple haemothorax, to the production of an initial pneumothorax of transitory duration; the blood might be poured out with the lung already collapsed, and then, the air being absorbed, the case would ultimately become one of simple haemothorax. The occurrence of contralateral massive collapse after wounds limited to the parietes, and where there was no penetration, showed that most extensive collapse could occur as a result of non-penetrating wounds, and therefore it is not necessary to invoke the hypothesis of transitory pneumothorax in order to explain the presence of collapse in haemothorax.

The writer is inclined to regard collapse of the lung in gunshot wounds of the chest as a phenomenon due directly to the injury of the chest, and although often accompanied by haemothorax, yet when so associated as not necessarily due solely to the latter. The most easily recognized cases of massive collapse are those associated with non-penetrating wounds of the chest-wall, and more especially those where the collapse occurs on the side opposite to that injured, and where it involves the entire lung. In such cases the diagnosis is easy, as the clinical picture is very definite, but other forms are by no means so easy to recognize, since if they are of the contralateral variety the area involved may be small, and the signs resemble those of pneumonia; and if they are of the homolateral type, other difficulties arise. Thus the homolateral variety is often associated with haemothorax, and much difficulty may be experienced in differentiating the physical signs of collapse from those due to other causes, such as fluid in the pleura, or consolidation of the lung, due to haemorrhagic infiltration of the lung produced, either directly by the missile lodged in or perforating the lung, or indirectly, merely as a result of the impact of the bullet on the chest-wall. Further, in the contralateral variety, when this is associated with haemothorax on the injured side, there may be difficulty in interpreting the significance to be attached to displacement of the heart, whether it is mainly due to the haemothorax or whether it is due to the supposed contralateral collapse. For these

reasons it is important to recognize that the typical examples of massive collapse in gunshot injuries of the chest should be sought for in cases of non-penetrating unilateral wounds of the chest-wall, and on the side opposite to that wounded; but massive collapse is by no means limited to such cases.

In civil practice massive collapse of the lung has been described by several observers, and more especially by Pasteur,<sup>1</sup> as occurring in a number of conditions; the best-known variety is that seen after certain abdominal operations and injuries. Pasteur has also described it in cases of death from diphtheritic paralysis, and in these cases it has been thought to owe its origin to paralysis of the diaphragm. Although the condition described in the present communication has great analogies with that described in civil practice, it is perhaps not certain that it is identical with it. In certain diseases, especially enteric fever and pneumonia, extensive collapse of the lungs is sometimes seen, and this may sometimes be not only lobar in its distribution, but also unilateral, so that it greatly resembles massive collapse, or is indistinguishable from it. More usually, however, it is not strictly lobar and involves more especially the posterior rounded portion of the lung that occupies the most dependent part of the chest in the recumbent posture. Such cases are well known and are quite different from those here described. Only one case of massive collapse, involving the whole of one lung, had fallen under the observation of the writer prior to the War, and in this case the cause was simple, i.e. the impaction of an acorn in the left bronchus. The expulsion of the foreign body by a violent fit of coughing was followed by a complete recovery.

It is difficult to form an opinion as to the frequency of occurrence of massive collapse. In civil practice, if the cases occurring after abdominal operations be excluded, it would seem to be extremely rare unless there is some obvious lesion interfering with the expansion of the lung, e.g. palsy of the diaphragm, foreign body in the bronchus, &c., and, as mentioned above, no case has ever fallen under the observation of the writer during a long hospital experience.

During the present campaign, on the other hand, a considerable number of cases have been seen; but here, also, it is not possible to give figures as to the frequency of its incidence, owing to the outstanding fact that it is so often not recognized unless specially sought for, so many of the patients do not present any urgent symptoms, and if symptoms are present the signs are often wrongly attributed to pneumonia. Most of the cases on which this paper is founded have been patients suffering from gunshot wounds of the chest, but typical cases of extensive massive collapse have been seen as a result of other wounds, more especially wounds of the buttock and wounds of the pelvis. In a few cases it has occurred as a complication of wounds of the thigh. No case is included where the wound was one of the abdomen. No opportunity was afforded the writer to see any large series of abdominal wounds; and further, such cases are not suitable for the study of a chest condition like collapse. For these reasons

<sup>1</sup> Pasteur, *Brit. Journ. of Surgery*, i, No. 4, 1914.



the present communication contains no facts as to massive collapse in abdominal gunshot wounds.

The term 'collapse of the lung', unless qualified, is used in this paper in the sense of a collapse of the lung more or less extensive, where there is no gross lesion such as fluid or air in the pleura to account for its presence. The collapse present in association with haemothorax is not fully dealt with, except in the cases of massive collapse of the entire lung in association with a small haemothorax. In the study of contralateral collapse it is essential to consider especially cases of unilateral gunshot wounds of the chest, and even then much care must be taken to determine whether a bilateral chest lesion has not really been produced, or even a contralateral one, as sometimes a bullet will pass through one side of the chest without producing any appreciable lesion on that side, and yet produce serious lesions on the opposite side. These difficulties, however, are not present in cases of unilateral non-penetrating wounds of the chest-wall.

## II. *Varieties of Massive Collapse.*

Collapse may involve only a portion of one lobe of the lung, or an entire lobe, or even one entire lung. In cases of unilateral gunshot wounds of the chest, it may be present either on the injured side only, or on the opposite side only, or on both sides. It may apparently vary in the degree of its development, as well as in the extent of lung involved; but this is often difficult to determine with any degree of accuracy, since only comparatively rough clinical methods are available for this purpose. At any rate, homolateral, contralateral, and bilateral collapse may be recognized, and it may be partial, lobar, or total, meaning by total a condition where the whole of one lung is involved. In some cases the condition seems to increase whilst the patient is under observation; in other words, it is progressive, involving first a small portion and then later a larger area of the lung. This, however, is rare, and certainly, in the cases where the whole of one lung has been affected, the entire lung has usually been involved when the patient was first examined and the condition recognized.

In the slighter forms, where the collapse is at first limited to a portion of one lobe, it is not very unusual for the area of lung involved to increase in size and so cause a considerable increase in the area in which physical signs are present. There is another form of variation that may occur in all varieties of massive collapse; in this the area involved does not increase in extent, but the affected lung becomes either less or more airless. The physical signs present are not found, in these cases, to extend and involve a larger area of lung, but they alter in character whilst remaining limited to their original area. Thus, at a first examination, the only abnormal signs may be weakness of the breath-sounds over a certain region, and were it not for the presence of other signs, and especially displacement of the heart, the correct interpretation of the weakened breath-sounds might not be arrived at. Then, after the lapse of some hours, these signs are replaced by others, such as loud tubular or even amphoric breath-



ing, showing that certain bronchial tubes are now pervious, and that the respiratory movements are adequate to cause the entry of air into the lung. In other instances the reverse change takes place, and weakened breath-sounds are only heard over an area where previously loud tubular breathing had been present. These variations in the degree of collapse are probably of mixed origin, sometimes depending on varying degrees of bronchial obstruction, and perhaps in other cases dependent upon a return of efficient respiratory movements.

Massive collapse involving the whole of one lung is the form that is most easily recognized clinically, inasmuch as the physical signs of this condition are extremely well marked. Two varieties have been met with, both associated with unilateral wounds of the chest. In the first, or homolateral form, the massive total collapse is on the same side as the injury, and in cases of perforating wounds may be accompanied with a small haemothorax. In the second, or contralateral variety, the collapse is on the side of the chest opposite to that wounded, and the wound in all these cases has been a non-penetrating one, limited to the parietes, and not causing, either directly or indirectly, any injury to the pleura, lung, or abdominal viscera. No case of massive collapse involving the entire lung on the side opposite to that wounded has fallen under my observation when a haemothorax was present on the injured side. Whether such cases occur or not, I do not know, but it is possible they occur and that life is not maintained sufficiently long for such patients to reach a hospital on the lines of communication. The contralateral variety of massive collapse involving the whole of one lung is a very remarkable condition, more especially as in many cases the wound on the opposite side of the chest is not only non-penetrating but may be trivial in character, causing no fracture or indeed any extensive injury of the chest-wall. Further, the clinical picture is a simple one, since there are no visceral lesions on the injured side to complicate the physical signs. In such a case the displacement of the heart may be extreme, yet no lesion exists on the injured side capable of displacing it, and thus it is easy to recognize that this displacement is not due to any pushing of the heart over from the accumulation of fluid or gas, but that it is due to the drawing over of the heart owing to collapse of the lung on the side opposite to the injury.

In the homolateral variety the clinical picture is not so simple, and such cases may readily be misinterpreted as cases of haemothorax with rapid absorption of the fluid, as this is often held to account for the fact that the physical signs alter rapidly, and may disappear in a few days.

Massive collapse of the lobar type, partial or complete, is a more common accompaniment of chest wounds, and it may be either unilateral or bilateral in its distribution. The bilateral variety may exist in cases of unilateral wounds of the chest. The contralateral form is a not infrequent complication of haemothorax, but no case has as yet been seen in association with pneumothorax, a fact perhaps not without significance with reference to any theory of the mode of production of collapse.

In lobar collapse the lower lobe of the lung is the part most often affected,

but cases have been seen where the collapse was limited to the upper lobe, and contralateral collapse may affect the upper lobe alone.

When the lower lobe is involved the physical signs do not suggest that the lesion necessarily begins or is most marked at the extreme base, but rather in the middle third, or even near the apex of the lower lobe. Owing to the upward displacement of the diaphragm and the altered anatomical relations, it is difficult to speak with exactitude as to this point. In the cases where the collapse is partial and involves only a portion of the lower lobe, the upper and middle thirds of the lower lobe are most frequently affected. In some of these cases the collapse is progressive, and ultimately involves the entire lower lobe. Bilateral collapse is, on the whole, uncommon, and usually involves relatively small areas in the lower lobes on both sides, or possibly the entire lower lobe on one side and a portion of its fellow on the opposite side.

### III. *The Physical Signs of Massive Collapse.*

The difficulty in the interpretation of the physical signs present depends in part on whether the massive collapse occurs in association with haemothorax, or whether it is the sole lesion produced by the chest wound. It will, therefore, be convenient to consider these signs first in cases where there is no haemothorax present.

(a) *Haemothorax absent.* The physical signs are usually well marked and easily recognizable, but sometimes, as will be discussed more fully below, the diagnosis may be difficult. The signs are most marked and most easy of recognition in cases of collapse involving the whole of one lung and of the contralateral variety. In such a case the patient presents a non-penetrating wound of the chest-wall limited absolutely to one side, so that there is no question of a foreign body having penetrated and lodged on the side opposite to the point of entry. In some instances the foreign body has been found in the wound, or removed by a simple incision, and direct evidence obtained that the wound is one strictly limited to the chest-wall. Physical examination shows that there is no lesion of the pleura or lung on the wounded side, and this is confirmed by X-ray observation, but very marked and obvious physical signs are found on the opposite side of the chest. Thus, the cardiac impulse, instead of being in its normal position, is displaced towards the affected side or even felt in the axilla, and is also displaced upwards. It may be visible and palpable as high as the third space, and a lateral displacement of two or three inches is by no means rare. The cardiac displacement is most easily observed in the cases where the collapse involves the left lung, and then may be in the axilla, but in right-sided cases the impulse may be detected in the neighbourhood of the right nipple line. The area of visibility of the cardiac impulse may be considerably increased in extent. The affected side of the chest is retracted and immobile, and the dome of the diaphragm on this side is abnormally high and also immobile. The high level

of the diaphragm is readily detected in the left-sided cases by percussion. On the right side percussion is not so reliable, but X-ray observation yields unequivocal evidence both as to its position and its immobility. Further, physical examination shows that the cases may be divided into two groups. In both, dullness on percussion is present that may extend as high as the clavicle, but in one group the tactile vocal fremitus is diminished or absent, and in the other it is increased. If diminished or absent, the breath-sounds are also diminished or absent, but if the vocal fremitus is increased, then the breath-sounds are loudly tubular or amphoric in character, and bronchophony and pectoriloquy are also extremely well marked. In the majority of cases, even when the cardiac displacement is extreme, the signs conform to the type with increased vocal fremitus and tubular breathing. In other words, the physical signs in the lungs are those commonly attributed to pneumonic consolidation, but, if anything, the signs are even more marked, especially the tubular and amphoric character of the breath-sounds. No real distinction can be drawn between the character of the tubular breathing heard in cases of massive collapse and that present in cases of pneumonic consolidation, but it is possible that the amphoric or hollow character of the sound is more often heard in massive collapse than in pneumonia. Some observers have expressed the opinion that the tubular breathing of consolidation differs from that heard over compressed or collapsed lung, in that in the latter conditions the tubular quality of the sound is heard mainly during expiration, whereas in consolidation it is equally inspiratory and expiratory. This distinction cannot, in my opinion, be maintained, at any rate in so far as concerns massive collapse. One of the main reasons why massive collapse of the lung is so frequently overlooked, is that the tubular breathing is so extraordinarily well developed that its mere presence is at once regarded as conclusive evidence of the existence of pneumonic consolidation. Due regard is not paid to the other signs present, and, more especially, the significance of the cardiac displacement is not recognized.

In some cases, however, dullness on percussion, diminished or absent vocal fremitus, and weakened or absent breath-sounds are the only lung signs present. These cases may also be difficult to interpret when first seen, unless adequate stress is laid on the position of the cardiac impulse. Speaking broadly, these signs are more usually present in the cases seen early, and the later cases tend to show tubular breathing, with increased vocal fremitus. One and the same case, however, may have the one set of signs at one period and the other set at another time, without any material change in the position of the cardiac impulse. Thus, one examination may reveal only weak or absent breath-sounds, and twenty-four hours later loud tubular breathings may be heard over the same area. The cases where tubular breathing is the leading sign are much the easiest to recognize; but it is quite possible that the other group, with the less obvious signs of mere weakness of breath-sounds, is really the more frequent. More observations are required in reference to this point. The signs may not only alter in one and the same case, as just mentioned; but this alteration may occur more than once, the

weak breathing being replaced by tubular breathing, which disappears to be followed by weak breathing. In such instances there is some resemblance to the well-known signs so characteristic of bronchiectasis, and it is probable that the variations in the signs are dependent on changes in the patency of the bronchial tubes. These recurrent variations are only seen in the later stages of the condition when the chest-wall is no longer immobile, and when there is some degree of re-expansion of the collapsed lung.

Râles and adventitious sounds may be present, but they are often absent throughout the entire duration of even the most extreme cases involving the whole of one lung. On the other hand, they are sometimes abundant, especially in the later stages, when the lung is re-expanding. They are also well marked in the rarer instances, when inflammatory complications develop in the collapsed lung; in fact, the presence of adventitious signs is rather to be associated with re-expansion of the lung or the development of inflammatory complications—they are not essential signs of massive collapse as such.

Displacement of the cardiac impulse is perhaps the most characteristic physical sign of massive collapse of the lung; in fact, this condition cannot be diagnosed with certainty unless this sign is present. The displacement is towards the collapsed lung, and is usually very considerable in amount. In collapse of the left lung, it is not unusual for the cardiac impulse to be felt at its maximum in the mid-axillary line, and in collapse affecting the right lung the impulse can be readily felt in the right nipple line. The patient is not conscious of the cardiac displacement, and does not present any cardiac symptoms. Although the displacement is so great in amount, it is sometimes, even when very marked, of transitory or of short duration, and hence considerable changes in the position of the impulse may occur in periods as short as twenty-four or forty-eight hours. This is not always the case, and the return of the heart to its normal position may be very slow and take as long as three or even four weeks; more usually, however, the return to normal takes place in about ten days. In the cases of extreme displacement of the heart, the signs in the lungs are usually not only well marked, but are of the type characterized by the presence of tubular breathing, increased vocal fremitus, together with bronchophony and pectoriloquy. This, however, is not invariable, and extreme displacement may occur, accompanied only with weak or absent breath-sounds at the base towards which the heart is displaced. This is important, since were it not for the cardiac displacement the physical signs present might well escape full recognition. Thus, in one case of a contour wound of the left chest, where the patient presented no urgent symptoms of any kind, the apex beat was found to be in the right nipple line, but the signs at the right base were little more than weakened breath-sounds. These signs were so ill marked at the first examination as to suggest the possibility of the case being one of dextrocardia. Twenty-four hours later, the signs at the right base were well marked, the tubular breathing being very distinct, and the case was clearly one of massive collapse. This was confirmed by X-ray examination and by the subsequent course of the case, since the heart

returned to its normal position, and at no time was there any lesion of the left pleura or lung.

Although displacement of the heart is such a marked sign of massive collapse, and is often so great in amount, yet, so far as my experience goes, it is not accompanied with the presence of basal cardiac murmurs, although such murmurs have been thought by many to result from mere displacement.

The displacement of the heart is mainly lateral, but in cases where the collapse involves either the whole lung or the upper lobe, there is also displacement upwards, so that the maximum impulse may be felt in the third space or behind the third rib. This upward displacement is more easily observed in cases of collapse involving the left lung.

The heart returns towards its normal position before the signs in the lung have disappeared, and it is by no means uncommon for the impulse to reach its normal site, whilst there is still an area of variable size in the scapular region where dullness and tubular breathing are still present, and these lung signs may persist for three or four weeks in some cases.

The persistence of such signs as tubular breathing, bronchophony, and pectoriloquy, at a time when the heart has returned towards its normal position, or even has reached it, is further evidence that the most important auscultatory sign of massive collapse is either weakness or absence of breath-sounds, since signs such as tubular breathing and bronchophony can evidently be extremely well marked when the degree of collapse is no longer great nor the area involved large. In other words, a small area of collapse, not sufficient to cause marked displacement of the heart, may, provided bronchial tubes of a suitable calibre are patent, give rise to extremely well-marked physical signs.

Weakness of the breath-sounds is a sign that may be due to many causes, and thus it often does not attract the attention it deserves; but in cases of massive collapse it derives its importance from the signs associated with it, especially the retraction and immobility of the chest-wall, together with the displacement of the heart and diaphragm. Considered by itself, it would often be difficult to appraise its true significance, but its associated signs reveal at once that it is really due to complete cessation, or great diminution, of the movement of air in and out of the affected lung.

Although the physical signs are most marked and most easily interpreted in cases of massive collapse involving the entire lung, yet they are also comparatively easy to recognize in cases of collapse involving an entire lobe (usually the lower lobe) on the side opposite to that wounded, and where the wound is single, unilateral, and limited to the parietes. In such cases the signs are essentially similar to those just described, except that they are more limited in area and correspond to the lower or upper lobe as the case may be. The cardiac displacement, although always well marked, is not so great as in cases of collapse involving the entire lung.

(b) *Haemothorax present.* When massive collapse occurs in association



with haemothorax in cases of unilateral wounds of the chest, it is much more difficult to recognize, and this applies both to the homolateral and the contralateral varieties.

*Homolateral massive collapse.* In this variety, although only a small basal haemothorax is present, the physical signs involve the whole of the wounded side. Dullness, weak or tubular breath-sounds, may extend as high as the clavicle, and unless care is taken to avoid the error, it may be thought at first that there is a very large collection of fluid in the pleural cavity. Examination may reveal, however, that the cardiac impulse is not displaced outwards, but that it is either normal in position, or, in many cases, actually displaced towards the affected side, instead of away from it. The position of the cardiac impulse is not consonant with the extensive physical signs being really due to a large amount of fluid in the pleura. Further examination shows the chest on the affected side to be retracted to a greater or less degree, and immobile, and the diaphragm is also found to be high and also immobile on that side. Another very important point is the fact that the physical signs alter rapidly, and in the course of a few days, sometimes even of a period as short as twenty-four or forty-eight hours, the lung becomes again expanded, and the only signs present are those indicative of a quite small effusion at the base. Such cases are not infrequently interpreted erroneously as instances of the rapid absorption of the bloody exudate from the pleura. There is no evidence that the pleura can absorb blood in the short periods that elapse in these cases, and conclusive evidence that the condition present is really collapse and not a large haemothorax is afforded by X-ray examination, quite apart from the fact that the peculiar and transitory physical signs present are fully and adequately explained by the presence of collapse. Further, in many cases, exploratory puncture has shown no fluid over the region where the signs were marked.

*Contralateral massive collapse.* In cases of unilateral haemothorax, no case of massive collapse involving the entire lung on the opposite side has been seen, and it is probable that such cases, if they occur, would not survive sufficiently long to reach a base or line of communication hospital. On the other hand, cases of contralateral lobar collapse are by no means uncommon, although the diagnosis of such cases is often difficult. The reason of this difficulty is obvious, since the displacement of the cardiac impulse is the physical sign of most significance in the diagnosis of massive collapse, and when haemothorax is present any cardiac displacement will naturally be attributed to the haemothorax, and thus the physical signs in the lung are regarded as due to the existence of a contralateral pneumonia when their true cause is a contralateral lobar collapse. In most cases the absence of the symptoms of pneumonia, together with a rapid change in the position of the heart, without any treatment such as paracentesis of the haemothorax, reveal the true nature of the case. Further, retraction and immobility of the lower chest, together with the upward displacement of the diaphragm, are signs that assist very materially in the diagnosis. The existence of contralateral collapse and its subsidence are very important factors in causing



rapid alterations in the position of the heart in cases of haemothorax where no paracentesis has been performed.

In some cases of contralateral collapse associated with haemothorax the physical signs are only found over a limited area, between the vertebral border of the scapula and the spine, corresponding roughly with the middle third of the lower lobe of the lung. This area is the same as that in which the signs remain most persistently in cases where originally the collapse involved either the whole of one lobe, or even the entire lung. It would seem, therefore, that this is an area in which the signs are not only most readily recognized, but also where they are most lasting.

In this description of the physical signs associated with massive collapse we have, so far, more especially considered the following types: Contralateral collapse, either total or lobar, the former as yet only seen with unilateral parietal or contour wounds, the latter occurring as an association not only of unilateral contour wounds, but also of unilateral penetrating wounds, causing a haemothorax on the wounded side.

Homolateral massive collapse, involving the entire lung, and associated with a small and negligible haemothorax, has also been described. But there is yet another form of massive collapse that merits attention, as it produces a remarkable clinical picture. In this last variety, as a result of a unilateral penetrating wound, a haemothorax of moderate or even of a large size is present, yet the following are the physical signs observed: The chest on the injured side is markedly retracted and immobile, there is dullness on percussion, with increased vocal fremitus, together with extremely loud tubular or amphoric breathing, and bronchophony and pectoriloquy are well marked. The diaphragm is raised on the affected side, but the heart's impulse is displaced away from the injured side; it may be as much as two inches from its normal position. The striking feature of these cases is the fact that, notwithstanding the retraction of the chest-wall on the injured side, the heart is displaced in a direction similar to that seen in pleural effusion, i.e. away from the affected side. This is the only variety of massive collapse in which the heart is not displaced towards the affected lung, and the reason is, of course, that the collapse is accompanied by the presence of a considerable amount of fluid. The importance of this type of case lies in the fact that the presence of even considerable amounts of haemothorax fluid, instead of leading to bulging of the chest with cardiac displacement towards the opposite side, causes, it is true, the cardiac displacement, but this is associated with marked retraction of the chest-wall over the pleural fluid. In some cases this chest retraction is only of temporary duration, and with a further increase in the pleural exudate, owing to the presence of infection, the side becomes bulged, and the case then presents the ordinary signs of a large pleural exudate. Such cases would seem to support the view that the collapse present in cases of haemothorax cannot be regarded as merely dependent upon the presence of the fluid in the pleura, since, if this were so, it is not clear why retraction of the chest-wall should be such a marked feature.

The study of cases of pure massive collapse, without haemothorax, whether contralateral or homolateral in type, serves to interpret the phenomena seen in cases of simple haemothorax, although in these cases of haemothorax the clinical picture is necessarily more complex. The actual signs present in any case must depend, to some extent, on the relative proportion of fluid on the one hand, and massive collapse on the other, and these factors are of special importance in determining the position of the heart.

#### IV. *Symptoms.*

The symptoms vary considerably in severity in different cases, and certainly do not seem to be dependent upon the extent of the massive collapse present, since cases where the whole of one lung is involved may be seen where the patient has few, if any, symptoms, provided he is in bed and at rest.

In most cases there is some dyspnoea, usually moderate in amount, but markedly increased on slight exertion, such as sitting up in bed, or turning over on one side, and the respirations may be somewhat increased in rate. No undoubted instance of the severe and urgent dyspnoea simulating that seen in pulmonary embolism has been seen; but in one case, where urgent symptoms of this type developed, they may have been due to massive collapse. In this instance, in a case with a large sterile haemothorax, very urgent dyspnoea supervened with great suddenness, together with signs of apparent consolidation on the side of the haemothorax. They ultimately subsided with no special treatment, and it was very improbable that they were due to pneumonia, and they were certainly not due to infection, as the patient recovered after paracentesis. The case, however, cannot be regarded as one in which the existence of massive collapse was proved. It is remarkable that urgent symptoms have always been absent in the cases of collapse involving the whole of one lung of the contralateral type, associated with contour wounds. In many of these cases the patients have only suffered from slight cough and dyspnoea. In some there has been some expectoration, but in several of the most marked examples of the condition there has been no expectoration at all. On the other hand, where the collapse is less extensive, e. g. contralateral lobar collapse, a more or less copious muco-purulent expectoration sometimes develops, and may persist for several days. The expectoration may somewhat resemble that of purulent bronchitis, but it is usually more watery and by no means so copious. A rusty sputum has never been present in any case diagnosed as massive collapse, except when pneumonia affecting the collapsed lung has occurred as a complication, and this sequel has been observed in several instances, and on two occasions has been confirmed on post-mortem examination. It is important to recognize that massive collapse may run its whole course without the presence of any expectoration, and with little or no cough.

The *duration* of massive collapse is variable; in some cases the signs not only alter, but may even clear up within a few days. Thus the heart may return

towards its normal position after a displacement of the impulse of as much as two inches in from one to three days, but it is of some interest that, even in these cases where the return of the heart to its normal position is not only rapid but also complete, some signs of the pulmonary collapse may persist, such as retraction, limitation of respiratory movement, and a localized area of tubular breathing. The more usual course of these cases is much slower, and the return to the normal takes place gradually, and is not usually complete until the lapse of three weeks from the onset; in some cases it may even be longer. The immobility of the side disappears, and limited or imperfect expansion takes its place; the apex beat returns gradually, and over the area of lung collapse the breath-sounds become less tubular. As the re-expansion of the lung takes place, adventitious sounds may become very abundant, especially crepitations, fine or medium in character, and râles, and these signs often present a considerable resemblance to those heard in a resolving pneumonia. During this stage of re-expansion, cough and expectoration are often present, but not invariably the expectoration is usually watery and mucoid, sometimes purulent, but never rusty. In exceptional cases it may not only be watery but also abundant, and rather suggestive of oedema of the lung, but true oedema of the lung has not as yet been observed post mortem in such cases; on the other hand, such lungs show evidence of marked congestion.

#### V. *Complications.*

Certain complications may supervene, and involve the portion of the lung affected with massive collapse; bronchitis, pleurisy, and pneumonia are definite and certain inflammatory complications that may occur, and of which clear clinical and post-mortem evidence has been obtained. It is probable that in some cases oedema of the affected lung develops as a complication, but the evidence of this is not as yet complete, although, as mentioned above, certain physical signs seen during the stage of re-expansion of the lung, and associated with a copious mucoid or watery sputum, are very suggestive of the presence of oedema.

Purulent bronchitis undoubtedly occurs as a complication, as it may be limited to the collapsed lung. In fact, this is the main reason for regarding it as a complication and not as a causative factor in the production of the collapse. The presence of purulent bronchitis limited to, or better marked in, the collapsed lung, as seen post mortem in cases of massive collapse, is a fact in striking contrast to the now well-known fact that where purulent bronchitis develops as a complication of haemothorax there is usually far less bronchitis in the lung beneath the haemothorax than in its fellow. The lung collapsed in association with haemothorax is not prone to develop inflammatory complications, but the lung of massive collapse may and frequently does develop such infections.

Pleurisy is not uncommon as a late complication of massive collapse. It is usually of the dry variety, giving rise to a friction rub; but effusion may occur, and in one case this was sufficient in amount to render paracentesis advisable.

Usually the effusion is very moderate in amount, and the correct interpretation of the case would be difficult, unless it had been under observation prior to the onset of the effusion.

*Pneumonia.* Two cases of lobar pneumonia supervening as a complication of massive collapse have been observed, and in both cases the pneumonia was limited to the collapsed lobe, and the patients had been under observation for many days prior to the onset of the pneumonia with typical physical signs of massive collapse of the lower lobe. When the pneumonia developed the heart's apex beat returned towards its normal position. One case was fatal, and at the post-mortem examination lobar pneumonia, in the stage of uniform grey hepatization, was found, but the lobe involved was still, notwithstanding the pneumonic consolidation, distinctly smaller than its normal size.

#### VI. *Diagnosis.*

The difficulty in the diagnosis of massive collapse varies greatly in different cases; the most sharply defined clinical picture is that seen in a unilateral non-penetrating wound of the chest, where massive collapse of the entire lung is present on the side opposite to that wounded, i.e. contralateral massive collapse. On the other hand, a small area of contralateral collapse occurring as a complication of a case of infected haemothorax may be difficult to distinguish from a contralateral pneumonia. This arises from the fact that pyrexia and bloody sputum may both result from the injury to the chest and lung on the wounded side, and not from the supposed pneumonia. Further, the cardiac displacement is apt to be attributed solely to the haemothorax pushing the heart over, when in reality it is mainly dependent on the contralateral massive collapse. Notwithstanding the difficulties, the condition can usually be recognized with accuracy, provided its possible occurrence is borne in mind and care is taken during the examination of the chest. The position of the cardiac impulse, the size of the chest on the affected side, the immobility of the chest-wall locally or generally, together with the high level of the dome of the diaphragm on the affected side, are signs of the utmost significance and value. The following errors of diagnosis have been made in cases where the real condition present was contralateral massive collapse, involving either the whole lung or one lobe. In one case a subphrenic collection of gas and fluid was supposed to be present in order to account for the upward displacement of the heart and diaphragm on the side of the collapsed lung, whereas not only was there no abdominal lesion, but the wound was a trivial non-penetrating one of the opposite side of the chest, and the case made a complete and uneventful recovery. In another case a pneumothorax was supposed to be present on the wounded side in order to account for the great cardiac displacement, although the patient presented neither signs nor symptoms of pneumothorax, and the wound was one that did not implicate the pleura. In another case the collapsed lung was actually explored by excising a rib, as owing to the well-marked physical signs in the lungs, tubular breathing

and râles, it was supposed that the lung was breaking down and that a grave pulmonary lesion was present. In another case the displacement of the cardiac impulse was attributed to cardiac dilatation and the signs of pulmonary collapse entirely overlooked. Most of these errors would be avoided if proper attention were paid to the question of displacement of the cardiac impulse, and especially if all observers recognized that displacement of the cardiac impulse is not necessarily dependent upon the heart being *pushed* over, but that it may be due to its being *drawn* over. Or to put the matter more correctly, the morbid process leading to the cardiac displacement should be sought for, and may possibly be found on the side towards which the heart is displaced, rather than on the opposite and wounded side. Further, it must not be too readily assumed, even when a displacing agent such as a haemothorax is present on the wounded side, that this is the sole cause of the cardiac displacement present. If no signs indicative of a pleural lesion are found on the wounded side, careful examination of the opposite side should be made, if the cardiac impulse is displaced.

In most cases of massive collapse, the heart is not only displaced, but it is greatly displaced, and this fact alone should cause a most careful examination to be made on both sides of the chest, notwithstanding the existence of a simple unilateral lesion and even in the absence of urgent symptoms. One difficulty sometimes encountered is the fact that the pulmonary physical signs may be comparatively slight, even when the cardiac impulse is greatly displaced, and then sufficient importance may not be attached to them; thus, in collapse of the right lung, the impulse may be in the right nipple line, but the only signs at the right base in an early period of the lesion may be weakness or absence of breath-sounds. Such cases may at first be misinterpreted as instances of dextrocardia, but the lapse of a few days, or sometimes of hours only, reveals their true nature, as the signs alter, and ultimately the heart returns to its normal position. The upward displacement of the diaphragm is a sign of the greatest importance, and is easily detected on the left side by the greatly increased stomach resonance. This increased resonance may lead to error, in that it may be attributed to pneumothorax or to a subphrenic collection of gas. Such mistakes are readily avoided by paying attention to the direction of the cardiac displacement, and also from the fact that the affected side is retracted instead of being bulged.

When the massive collapse involves the entire lung, the displacement of the cardiac impulse is oblique, inasmuch as it is displaced vertically as well as laterally. This very characteristic sign is more obvious in cases of collapse involving the left lung. In collapse limited to the upper lobe of the lung, the cardiac displacement is also oblique.

In cases of homolateral massive collapse, especially if associated with a small haemothorax on the injured side, the diagnosis is often difficult, and two errors are more especially liable to be made. In the first place, a large haemothorax may be diagnosed owing to the extent of the physical signs, whereas in reality there is only a very small collection of fluid. The second type of error is more serious, and is especially apt to be made in cases where infection of the haemothorax is



present, and the patient consequently presents more or less urgent symptoms. In such a case the well-marked signs may lead to a diagnosis of pneumonic consolidation, and the symptoms due really to the infection of the pleural contents may be attributed to the supposed presence of pneumonia. If this error is made, valuable time may be lost, and the patient's chance of recovery gravely imperilled. The usually accepted signs of consolidation, i. e. dullness on percussion, increased vocal fremitus, and tubular breathing, are often extremely well marked in cases of massive collapse, and if, in addition to these, pyrexia, hurried respirations, and a bloody sputum are present, it is not surprising that a diagnosis of 'traumatic pneumonia' is made, whereas the true condition present is really a small infected haemothorax together with a large area of massive collapse. Such cases require immediate surgical intervention, and thus call for early exploration in order to determine whether fluid and infection are present in the pleural cavity. The retraction and immobility of the affected side are signs of value in the diagnosis of this type of case, but the position of the cardiac impulse varies, and is dependent upon the size of the haemothorax in association with the massive collapse. Thus, if the effusion is of some size, the heart may be displaced, as in ordinary pleural effusion, towards the sound side, but even then the presence of massive collapse may be detected owing to the retraction of the affected side. If the haemothorax is small, the heart may be displaced towards the affected side, and then the diagnosis of massive collapse is easy. In pneumonic consolidation the side affected is not retracted, and the cardiac impulse is not materially displaced, and certainly is not displaced towards the side affected.

The differential diagnosis between a large haemothorax and a small haemothorax associated with massive homolateral collapse involving the entire lung can also generally be made, owing to the presence of retraction of the chest-wall in the one case, and bulging in the other, and also because the heart is not only not displaced away from the affected side, but on the contrary may be displaced towards it. Further, in homolateral massive collapse the dullness extends right up to the clavicle, whereas even in the very largest haemothorax there is, at any rate in most cases if not in all, a small area of skodaic hyper-resonance in the uppermost intercostal space or spaces. Although the diagnosis of massive collapse can usually be made from a consideration of the physical signs alone, yet there are other factors that may be of help. Thus, in many cases of massive collapse involving the entire lung, the patient may present no symptoms beyond slight dyspnoea; in other words, although the physical signs are most extensive, symptoms are absent or slight in amount. This is in great contrast to what obtains when widespread pneumonia, or a very large haemethorax is present. It is true that in the earlier stages of massive collapse dyspnoea may be present, and even be urgent, and in the later stages, when re-expansion is taking place, a copious mucoid sputum is sometimes seen; but these signs are not invariable, and in the fully established condition all marked symptoms may be absent.

Pyrexia is a sign of very uncertain value; there is some evidence that it may



be associated with massive collapse, and it is certain that in a few cases pleurisy and pneumonia may occur as complications. Further, in any given case the pyrexia may be due to other causes, e. g. the state of the wound, the presence of an infected haemothorax, &c.; hence the presence of pyrexia cannot be regarded necessarily as evidence that the signs present are due to pneumonia rather than to massive collapse. The absence of pyrexia, however, when the signs are marked and widespread, is a factor of value and importance in the diagnosis.

For diagnostic purposes the physical signs may be divided roughly into three groups, corresponding to three stages in the progress of the case. In the first period the main physical signs are retraction and immobility of the affected side, together with weakness or absence of breath-sounds and displacement of the heart, often extreme in amount. In the second period the weakness of the breath-sounds has been replaced by loud tubular or amphoric breathing, together with increased vocal fremitus and loud bronchophony and pectoriloquy. In the third period, i. e. the stage when the lung is expanding, abundant râles and crepitations may be present over the area where tubular breathing is marked. In both the second and third stage the heart is still displaced, but, as already mentioned, the lung signs may sometimes persist over a small area at a time when the heart has returned to its normal position.

The recognition of contralateral massive collapse is most easy in cases of unilateral non-penetrating wounds of the chest and in cases of penetrating wounds, where the entry and exit wounds are in such positions as to prove that the injuries are confined to one side of the chest. In cases where there is only a wound of entry, and the position of the retained missile is doubtful, the difficulties of diagnosis are far greater. The presence of bilateral physical signs may be dependent upon the existence of direct lesions in both pleural sacs and their contents, as well as upon the presence of a unilateral injury and the subsequent development of a complication like massive collapse. In many of these cases it is not possible to diagnose with certainty between effusion and collapse without exploratory puncture of both pleural cavities. The position of the cardiac impulse is again the most valuable sign, since in bilateral haemothorax great displacement is not usual; hence if the signs suggest a moderate haemothorax on one side, and yet there is great displacement of the apex beat, it is probable that contralateral collapse rather than bilateral haemothorax is present.

X-ray examination is necessarily of great value, and should be used in all cases.

## VII. *Ætiology.*

Although this communication deals with massive collapse more especially in its relation to gunshot wounds of the chest, in any discussion as to its causation and nature it must be recognized that it also occurs as a complication of a number of other injuries, and, indeed, in certain diseases. In many of these

conditions, however, the problem is more complicated than in those where it follows an injury of the chest. Thus it is not infrequent in wounds of the abdominal wall, and also in wounds of the buttocks, pelvis, and thighs. Although undoubted instances have been met with in cases of gunshot wounds of the thigh, with fracture of the femur, it would seem to be a rare complication of this injury. In cases following wounds of the buttocks or pelvis, the wound is often of a severe character, and such cases are not very suitable for the study of the mechanism of its production, in that the wound is often of such a character as to have led to the patient being compelled to assume a constrained and unnatural posture for hours or even for days, and it is extremely difficult to determine how important a factor this may be in the production of the lung complication. It will suffice to say here that massive collapse, seen after these injuries, is essentially similar in character to that seen after injuries of the chest, and, therefore, that the condition is not to be regarded as solely produced by chest injuries. Further, two typical cases were observed in unwounded men where the condition occurred as a sequel to ordinary lobar pneumonia, and where it cleared up completely and rapidly, and was, therefore, not dependent upon any chronic inflammatory thickening of the pleura or any fibrosis of the lung produced by the pneumonia. These cases, however, will not be discussed further, and are only mentioned in illustration of the fact that the condition is not limited to injuries. Many cases of collapse as a result of abdominal operations, appendicitis, hernia, &c., have also been seen, similar to those described by Pasteur, but in these cases also the problem is complex owing to many factors, such as the influence of an anaesthetic, the presence of peritonitis, &c. As already mentioned, the writer has had no opportunity of determining the frequency of its occurrence as a complication of abdominal wounds, but it certainly occurs in wounds of the abdominal wall, buttocks, ilium, and thighs, where there is no lesion of the abdominal or pelvic cavities.

In wounds of the chest the outstanding fact is that massive collapse in its most extreme form, involving the whole of one lung, may occur as a sequence to a small wound limited absolutely to the chest-wall. Therefore injury to the lung is not necessary for its production. Further, it occurs not infrequently on the side of the chest opposite to that injured, even when the wound is of this trivial character, and the collapse involves the entire lung, and this is further evidence, if such is required, that injury of the lung itself is not necessary for its production. It may be completely developed in less than twenty-four hours after the infliction of the wound; how soon it develops after the wound is not known, but no case has been seen by the writer where collapse was known to be absent when the patient was admitted to hospital and subsequently developed. In other words, all cases had signs on admission, but very few cases have been seen earlier than twenty-four hours after being wounded. A few cases have been seen where the signs suggested that the lesion was progressive, but this is exceptional, and it is possible that the observations were not strictly accurate. The condition, even in its most extreme form, may occur without the patient

giving any history of expectoration either of blood or sputum, purulent or otherwise. Three points seem to be of importance in any discussion as to its causation, i. e. (1) that it may follow trivial injury of the chest-wall, (2) that it always occurs early, and (3) that there may be no expectoration at any stage in its evolution, and sometimes no urgent symptoms. When massive collapse is present the chest on the affected side is immobile, and the problem as to its causation would seem to centre round the significance to be attached to this immobility.

Is the chest immobile and retracted because the lung is collapsed, or is the lung collapsed because of the immobility and retraction of the chest-wall? This problem is difficult of solution from the study of clinical phenomena alone, and probably will require experimental methods before a satisfactory answer can be given; but yet some light may be thrown on the question by a discussion of the clinical facts. If the collapse is primarily of lung origin, the only obvious mode of production would seem to be that of obstruction of the bronchi. There is no evidence, in these cases of massive contralateral collapse involving the entire lung, of any gross obstruction of the larger bronchi. It is difficult to see how a unilateral injury, limited to the chest-wall, in a healthy man, could within twenty-four hours produce an obstruction of the main bronchus of the opposite lung sufficient to cause complete collapse of the lung, and yet that no urgent symptoms and no expectoration should be present. In cases where the wound is a penetrating one and involves the lung, there must always be the possibility that blood, perhaps in quantity, may have been inhaled into the opposite lung, and hence, in discussing the mode of production of massive collapse, only the cases of contralateral collapse with non-penetrating wounds are considered. Further, there is definite post-mortem evidence that massive collapse may be present, and yet no gross obstruction of the main bronchi is found. Hence obstruction of the main bronchi may be excluded as a common or probable cause of the condition.

The problem whether obstruction of the smaller bronchi, or bronchioles, is the essential factor is much more difficult. Such a mechanism would probably be a sufficient explanation of the condition, if we could surmise how it could be called into action. Massive collapse is not a condition produced by the more common and familiar causes of bronchial obstruction. Thus, in bronchitis in its many forms, where great obstruction to the finer bronchi is present, although collapse in limited small areas is common, yet passive collapse does not, so far as I know, occur; and in a considerable number of fatal cases of purulent bronchitis I have never seen it. Further, it is remarkable that so-called compensatory emphysema is not a marked feature of massive collapse, whereas it is a most characteristic accompaniment of the limited areas of collapse associated with bronchitis.

Again, certain varieties of asthma are supposed to be dependent upon bronchial spasm, but here, also, massive collapse is not a sequel. Finally, all forms of bronchial obstruction hitherto known always produce severe and often dangerous symptoms, and this is certainly not true of all cases of massive collapse,

even when they involve very large areas of the lung, or even the entire lung. The patient from whom Plates 10-12 were obtained was admitted to hospital on the evening of the day on which he had been wounded, and had massive collapse involving the whole of the left lung; he had no urgent symptoms and had walked four miles after being wounded.

Although it must be admitted that obstruction of the finer bronchi, produced perhaps by an increased tonic contraction of their musculature, might possibly be held capable of producing the condition, such an explanation is purely hypothetical, and there are, as mentioned above, grave clinical difficulties in the way of its acceptance.

There are also serious difficulties if the matter is considered from the standpoint of physiology. Thus any diminution in the volume of the lung, brought about by diminished pressure in, or obstruction of, the bronchial tree, immediately brings into play increased inspiratory action and increased inspiratory tonus. This mechanism is very probably the cause of, or one of the causes of, the production of so-called emphysema in such cases. In collapse retraction and immobility of the chest and of the diaphragm are not only leading phenomena, but are also early phenomena. They are not late and secondary results of the collapse; they are present in their most marked form in the cases when first seen, and they are very difficult of explanation on any hypothesis of the lung collapse being primary and dependent upon bronchial obstruction.

For these reasons it seems probable that bronchial spasm or bronchial obstruction cannot well be regarded as the cause of the variety of massive collapse dealt with in this paper, and more especially of massive contralateral collapse in non-penetrating chest wounds.

If the collapse is not primarily of bronchial origin, we must next consider whether it is probable that it arises as a result of the immobility and retraction of the chest-wall, and discuss further how this chest-wall condition itself arises. It is well known that inefficient expansion of the chest, however produced, is capable of causing collapse in varying degrees of the underlying lung. In some instances a constrained posture or prolonged recumbency is sufficient to cause quite extensive collapse, involving, for instance, one lobe of the lung. Pasteur, in his article on massive collapse as a complication, especially of abdominal operations, suggested that the inspiratory mechanism was in abeyance and that the expiratory muscles acted as actual deflating agents. There are difficulties in the way of the complete acceptance of this view, inasmuch as it is necessary to apply very considerable pressure to the exterior of the lung in order to expel the contained air, but accepting Pasteur's conclusion that the inspiratory mechanism is in abeyance in these cases, there is another way in which it is possible that collapse might be produced. If, as a result of the cessation of inspiratory movements, the chest became fixed in an extreme expiratory phase, the air in the lungs would not be adequately renewed, and the air present would be absorbed by the blood-stream and thus collapse might be brought about. The volume of the lung in massive collapse is always much less than that of the lung

during the most extreme expiration, and this also is a reason for thinking that something more than expiratory deflation is necessary for its production.

Physical and X-ray examination reveal that the chest-wall and diaphragm are immobile and in an extreme expiratory phase, the immobility of the diaphragm being especially obvious. A consideration of the following facts supports the view that the chest-wall condition is primary and not secondary to the lung condition. In certain cases of haemothorax, where homolateral massive collapse is present, the heart, as already pointed out in the section dealing with physical signs, is displaced towards the opposite side, and yet the affected side is retracted and not bulged. If the chest-wall condition was merely passive and only dependent upon the existence of the collapsed lung, it is very difficult to understand why the pleural effusion does not cause bulging of the side. The co-existence of retraction of one side, with displacement of the heart to the opposite side, certainly suggests that the chest-wall condition is an active and not a passive one.

The mode of production of this chest-wall condition remains most obscure. In ordinary wounds of the chest its presence might be regarded as somewhat similar to the state of the abdominal wall in abdominal injuries and diseases. It might even be regarded as of teleological significance and eminently a safeguard to the wounded lung. The phenomena of contralateral collapse, as a complication of trivial parietal wounds, is a very serious objection to any such explanation, as is also the occurrence of similar collapse as a result of wounds in distant parts of the body. The immobility and retraction of the chest-wall, even in the homolateral cases, are not dependent upon the presence of pain, &c., produced by the severity of the wounds, as the wound is often of a quite simple character. In the contralateral cases it is obvious that some more complex mechanism is at work, since no injury is present on the affected side. No case of contralateral collapse has fallen under my observation as a complication of pleural effusion, nor yet in pneumothorax, even when the latter has been the result of a gunshot wound. It is possible that it may occur in pneumothorax, but that such cases are rapidly fatal, or it may be that the urgent dyspnoea present in the early stages of pneumothorax prevents its development.

It would seem in the present state of our knowledge that massive collapse is a condition that may supervene at an early stage, after an injury of the chest or other part, and that the causative injury is not necessarily a severe one. Further, massive collapse in its most marked form, i. e. contralateral massive collapse involving the entire lung, may develop when the injury is not only trivial, but is also limited absolutely to the parietes. The collapse is more readily explained as a result of the immobility and retraction of the chest-wall and diaphragm, than if regarded as due to bronchial obstruction. The mechanism by which this condition of the chest-wall is produced is obscure, but possibly it is of reflex nervous origin.



*Contralateral Massive Collapse involving entire Lung from Non-penetrating Parietal Wound.*

Private R. G.—. Aged 41.

16.5.17. Wounded on the morning of 16.5.17. No haemoptysis. Walked four miles to dressing station, where a piece of shrapnel fell out of the wound on taking off his tunic. Admitted to General Hospital same evening. Several slight superficial wounds of skin and face and right back, one only involving deeper parts, 1" external to angle of right scapula, about  $1\frac{1}{2}$ " long, from which foreign body had fallen. No symptoms, and patient says he is quite well. Left side of chest immobile and heart displaced to left.

18.5.17. Left chest immobile. Heart's apex beat on level of nipple and 1" external to it, and 5" to left of mid-sternum. Whole of left chest dull on percussion as high as clavicle.

Resonance in Traube's space well marked. Tubular breathing, bronchophony, and pectoriloquy.

X-ray report: Considerable opacity over whole of left chest. No signs of fluid on right side. Right side diaphragm moving well, left side diaphragm immobile.

20.5.17. Chest explored by puncture both sides. On right side small quantity of bright blood, probably lung blood. On left side puncture at three separate spots; negative result.

21.5.17. Circumference of chest,  $34\frac{1}{2}$ " to 36". Right side,  $17\frac{1}{2}$ " to  $18\frac{1}{4}$ ". Left side, 17" to  $17\frac{3}{8}$ ".

Slight cough. Left chest moving slightly. Apex beat 5" to left of mid-sternum, and slightly above level of nipple. Dullness to second rib on left side. Breath-sounds feeble over left chest.

22.5.17. X-ray report: Left apex clearer and diaphragm on left side moving a little.

23.5.17. Abundant râles in vicinity of angle of left scapula. Temperature normal. Pulse 72.

24.5.17. X-ray report: Right diaphragm moving well, left only moving a little; level of diaphragm on this side at fifth costal cartilage.

26.5.17. X-ray report: Diaphragm moving well on both sides. Left lung clear almost to base. Heart still displaced. Left diaphragm at the level of fifth costal cartilage.

28.5.17. Impulse in fourth space  $\frac{3}{4}$ " external to nipple. Chest-wall still retracted and X-ray report gives level of left diaphragm at fifth intercostal space.

2.6.17. Some impaired resonance still present at angle of left scapula, with a small area of tubular breathing, increased vocal fremitus, and bronchophony. Normal anteriorly. No cough and no expectoration. Impulse in nipple line.

6.6.17. Evacuated to England quite well.

Three X-ray Plates. (1) 19.5.17. (2) 21.5.17. (3) 23.5.17.

*Massive Collapse of Left Lung following a Wound of Left Ilium.*

Private Basil H. S.—. Aged 22 years.

Wounded 26.9.16, and was lying out three days.

Dyspnoea immediately after being wounded.

Admitted to General Hospital on 2.10.16.

Entrance wound healed 2" inside anterior superior iliac spine on the left side. Exit 1" below crest of ilium and a hand's breadth from middle line.



Temperature normal. No abdominal signs or symptoms.

Respirations 30. Pulse 60.

Apex beat external to left nipple line.

Left chest retracted and movement very slight.

Resonance impaired, breath-sounds feeble.

Behind tubular breathing up to angle of scapula with bronchophony. No adventitious sounds. Slight cough and some mucoid watery expectoration.

6.10.16. X-ray report: Opacity over left chest, especially at the base. Heart displaced to left, and on left side diaphragm raised and immobile.

15.10.16. X-ray report: Translucency much increased on left side, but heart still displaced. Diaphragm moving on both sides.

This patient received no special treatment and the signs were so definite that the chest was not punctured. He was evacuated to England on 16.10.16, much improved and presenting no symptoms.

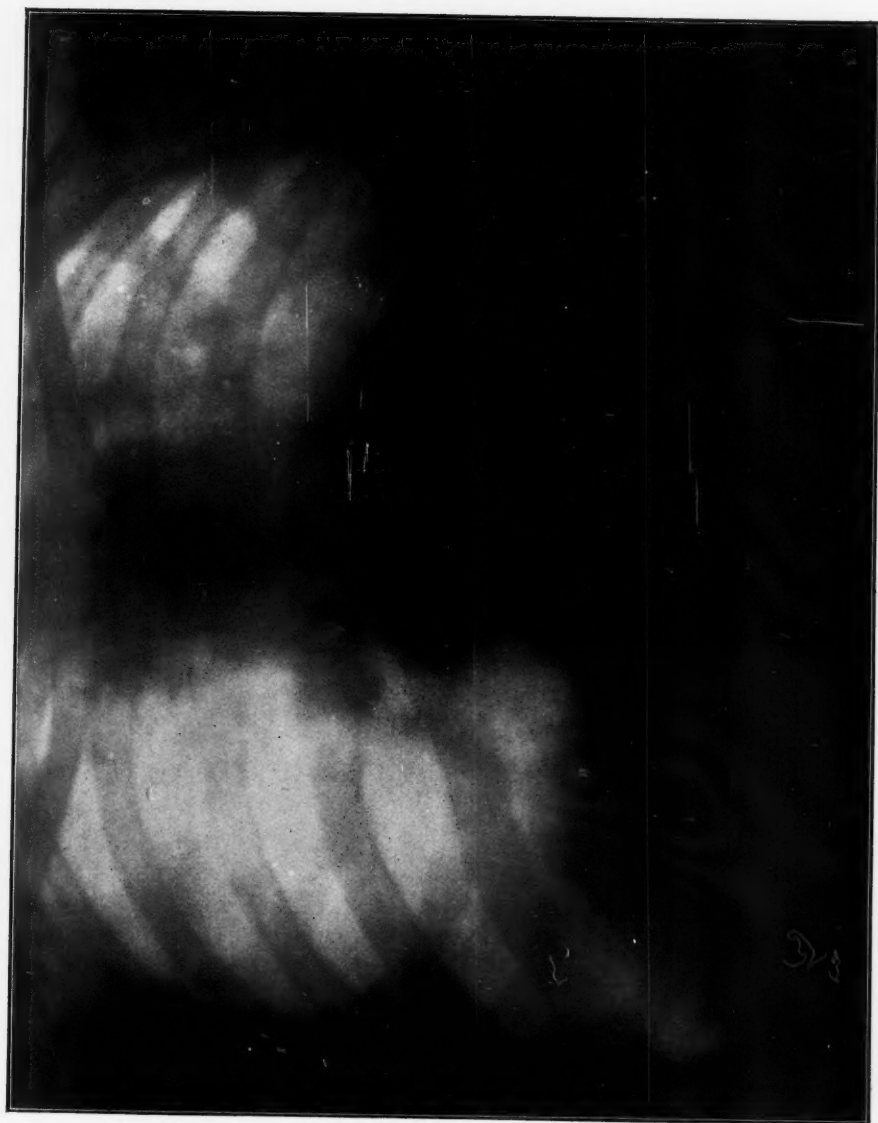
#### DESCRIPTION OF FIGURES.

PLATES 10, 11, 12. Three X-ray photographs taken in the sitting posture from the case of Private R. G—— quoted above.

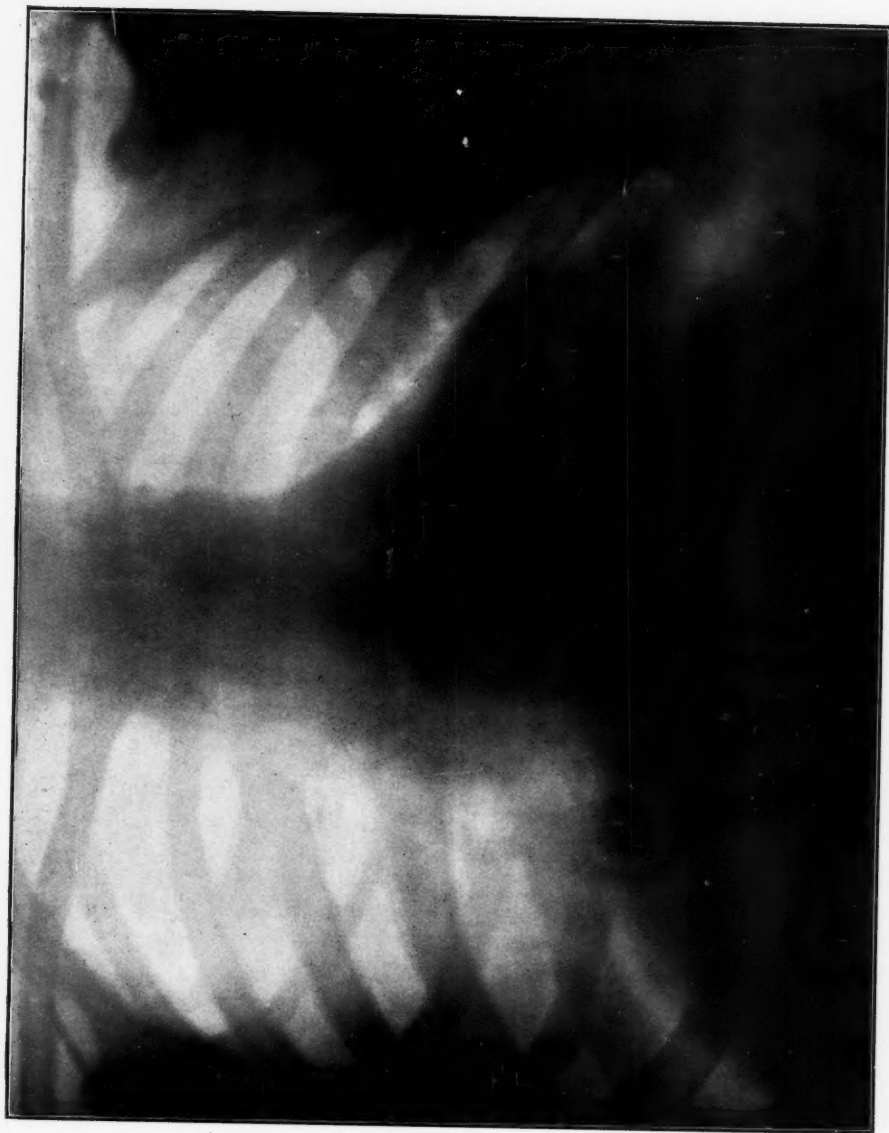
Plate 10 taken on 19.5.17. Plate 11 taken on 21.5.17. Plate 12 taken on 23.5.17.















## INTRATHORACIC PRESSURE IN HAEMOTHORAX, PNEUMOTHORAX, AND PLEURAL EFFUSION, AND EFFECTS OF ASPIRATION AND OF OXYGEN REPLACEMENT

BY GEORGE C. SHATTUCK AND E. S. WELLES

THE work to be described was undertaken in the hope of throwing light on the phenomena of haemothorax and allied conditions which might be useful for diagnosis or treatment. It is conceded that the observations are too few in number to permit of dogmatic conclusions. They are offered merely as a basis for tentative interpretation of clinical findings, and it is hoped that others will be sufficiently interested to take up the problems in question. The measurements of intrathoracic pressure were made with a water manometer graduated in centimetres.

### *Description of Manometer.*

The plan of the manometer is shown in Diagram I. It consists of a U tube of No. 3 glass tubing. The arms of the U are 45 cm. in length and between them is attached a centimetre scale. The zero point is in the middle of the scale and the numbers run to 20 above and below the zero. As the fluid in one arm goes down as far as it rises in the other a reading from either arm must be doubled to give the true figure. Positive or negative pressure, therefore, can be registered up to 40 cm. of water. The water in the manometer is coloured with fuchsin. From one arm of the manometer a rubber tube about eighteen inches in length leads to a glass connexion through which it is attached by a short piece of rubber tube to the needle or cannula.

When the manometer is to be used the glass connexion and short rubber tube are detached and sterilized. They are not reconnected with the manometer until the passage of air or of fluid through the needle shows that its point is free in the pleural cavity. If the manometer then fails to fluctuate with the phases of respiration it is assumed that the needle has slipped out of the cavity or has become plugged.

### *Testing the Manometer.*

Tests were made to show the errors of the method. Errors were found to be of two kinds: technical errors, which are avoidable; and mechanical errors, inherent in the apparatus. (See Diagram II.)

Two sources of technical error require mention. First, the needle used should not be smaller in calibre than a medium-sized aspirating needle. Needles of the size used ordinarily for the subcutaneous injection of serum may give readings, but they will be very unreliable. Second, when, by a positive pressure, fluid is driven into the tube leading to the manometer that part of the tube which contains fluid must be kept horizontal. If this is not done the fluid by its weight exerts an effect on the manometer.

The relative position of the parts of the tube which contain air only and the elevation of the manometer itself in respect to the needle have no effect.

Measurements of pressure in air with dry needle or cannula and dry tubes were found to correspond very closely with those obtained through a tube of the same calibre as that of the manometer.

The most important mechanical error was found where readings of pressure were taken below the surface of water. The actual pressure below the surface under atmospheric pressure was ascertained by measuring the depth of fluid above the point of the needle or cannula. Depths of 5 and of 10 cm. were tried. When the needle was used the readings under water were about 4 cm. too low. With the cannula they were slightly better. Positive and negative air pressures were then exerted alternately above the water and readings were made with needle and with cannula at depths of 5 and of 10 cm. The air pressure was determined by readings from the air in the top of the jar. The pressure at the needle was estimated by adding to the air pressure the depth of water above the needle.

For example :

Air pressure . . . . .	= +4 cm. or -4 cm.
Water pressure . . . . .	= +5 " " +5 "
Actual pressure at point of needle . . . . .	= +9 " " +1 "

The resulting figures compared with the pressure registered through the needle showed the mechanical error.

Positive and negative air pressures of from 5 to 15 cm. were used in the tests.

Negative air pressures, registered through the needle under water, showed errors of from 0.75 to 3.25 cm. too low, and positive air pressures errors of from 3.25 to 5 cm. too low.

The errors with the small aspirating cannula varied from 0.75 too high to 1.75 too low for negative air pressures, and from 3.25 to 7.75 cm. too low for positive air pressures registered under water. The readings which were too high occurred when the water pressure nearly counterbalanced a negative air pressure.

The larger errors were found with high positive air pressures exerted over a depth of 10 cm. of water. The positive pressures in these instances totalled more than 20 cm.—a condition seldom, if ever, met with in the chest.

In general, it may be said that the mechanical error under water causes readings to be roughly 3 or 4 cm. too low, but that it is less for negative than for positive pressure.

The mechanical error seems to be caused chiefly by the capillary attraction

of the water for the walls of the tube when the pressure is positive. When the pressure is negative the water hinders the escape of air from the manometer through the needle. Air escapes more easily through the cannula, so that the cannula is more accurate than the needle for negative pressures.

The viscosity of the fluid in haemothorax being greater than that of water, the errors of registration of pressure in this medium are probably larger.

Having found such serious defects in the instrument it may be doubted whether the observations made with it are of any value. It is believed, however, that something may be learned by comparison of the figures.

#### *The Tables.*

The recorded figures are intended to show, not the extreme limits of variations such as occur when the breathing is irregular or spasmodic, but the expiratory and inspiratory pressure in quiet breathing. If the breathing is shallow these fluctuations are small. Cough may give positive pressures above the capacity of the manometer to register, and an unusually strong inspiratory effort gives a high negative reading. The tables include no figures such as these.

It is unfortunate that in the earlier part of the work only one figure was recorded. This figure represented, as nearly as could be judged, the mean pressure. When these observations were tabulated the spaces for inspiratory and expiratory pressure and the excursion column could not be filled out.

The small sterile haemothorax has been taken as a standard, and, by so doing, differences of pressure due to the presence of large quantities of fluid, of air, or of gas in the pleural cavity have been eliminated from Table I.

This table shows in parallel columns, first, the observation number; second, the number of days elapsed between wounding and making the observation; and after that, in the following order, the pressure at inspiration, at expiration, the mean pressure, and the excursion of pressure due to the phases of the respiration.

The summary below the table indicates that the average mean pressure varies little during the first sixteen days, but that the excursion steadily increases. It may be inferred that absorption of a haemothorax is slow, but that respiratory movement of the injured side nevertheless begins early to increase.

Table II shows that larger haemothoraces tend to show higher pressures and smaller excursions. The mean pressure in some of these cases was positive. The mean pressure in all the small haemothoraces was negative. Atmospheric pressure was recorded in two of them during expiration, but no positive pressure was observed among them.

The number of satisfactory observations in Table III is too small to permit of any deduction. It is believed, however, on clinical grounds, that infection in the pleural cavity leads to increase of fluid and that this may cause a rising pressure. When gas is formed in considerable amount by bacterial action the rise of intrathoracic pressure is probably more marked and more rapid in development.

Table IV deals for the most part with haemopneumothoraces. The first case was infected, the others sterile. Nos. 32 and 33 apparently were uncomplicated by the presence of fluid. No. 34 is of interest as showing the pressure in the normal pleural cavity on the unwounded side. In this table the attempt was made to differentiate between measurements taken in the fluid and those taken in the air. No great confidence is to be placed, however, in the statements in regard to this because it is not easy to be certain which medium the needle was in at the time the reading was taken. Either fluid or air may often be drawn off from the same point by tipping the needle a little one way or the other, so that the fact that fluid was first drawn at a certain point does not prove that the needle-point was still in fluid a moment later when the manometer reading was made. In this connexion observation 35 is worth noting. It was believed at the time that the needle was in fluid when this reading was taken, but a glance at the high positive pressure in the expiratory column and the large excursion suggests that these high pressures were registered not in fluid but in air. The highest pressures hitherto met with have been found in large haemothoraces in which the excursion was small. Moreover, the tests of the manometer showed that the largest errors occurred when the attempt was made to register a high positive pressure below the surface of fluid, but that pressures in air were accurately recorded. Therefore, one might expect to get higher positive and lower negative pressure records from the air in pneumothorax than from the underlying fluid. If this reasoning is correct the low negatives of No. 41 as compared with the corresponding figures of No. 40 are anomalous, but the difference of excursion is as expected.

Tables I and II seem to show that the amount of reduction of the normal negative pressure in the pleural cavity is intimately related to the size of the haemothorax, and that, other things being equal, the greater the volume of the fluid the less negative pressure will remain.

There seems no obvious reason why the same should not hold true for pneumothorax or for the combined volume of fluid and air in haemopneumothorax. If this be the case degrees of displacement of the cardiac impulse, in the absence of disturbing factors such as adhesions or unusual mobility of the mediastinum, should give a rough idea of the volume of fluid, of air, or of fluid and air in the pleural cavity of the opposite side. To judge of the volume of fluid and air by other physical signs is most difficult, because the resonance of the air masks considerably the dullness of the fluid. But if, as some believe, a small amount of air associated with a haemothorax causes disproportionate displacement of the heart this sign also is of little value. Further evidence on this point would be of interest.

Some pressures recorded in cases of ordinary pleural effusion (Table V) were introduced for comparison with those of haemothorax. The mean pressures show marked differences which correspond, presumably, to differences in volume of fluid.

In the same table, but recorded in other columns, are pressures observed after aspiration. They give an idea of the extent of the changes of intrathoracic

pressure which take place after aspiration, and suggest that when a large quantity of fluid is to be withdrawn oxygen replacement might be used to advantage in pleural effusion, as it has been in haemothorax.

The method was used in one case of pleural effusion with success in preventing pain and cough. Similar observations were made in haemothorax and in haemopneumothorax (Table VI). They indicate that the amount of reduction of pressure after aspiration is dependent on the quantity of fluid or of fluid and air withdrawn.

The seventh table shows that existing pressure in the chest can be maintained by replacement with oxygen, and that the volume of oxygen required is no greater, and may be slightly less, than that of the fluid withdrawn. The records of some cases in which oxygen was used have been lost, so that the table is incomplete.

Two methods were used. In the earlier cases several hundred c.c. of fluid were withdrawn, and then enough oxygen was put in to restore the original pressure. Withdrawal of fluid and replacement with oxygen were then repeated alternately until no more fluid was obtained. It appeared that the volume of oxygen required to restore pressure was much less than that of the fluid withdrawn. Apparently expansion of the lung in the interval or some other internal readjustment took place. Later, by the method of Dr. W. Palfrey, fluid was withdrawn and oxygen put in simultaneously volume for volume. His apparatus has the advantage of simplicity, and it can be made in a few hours at any hospital from materials at hand. The method was devised by Dr. Palfrey while serving at a General Hospital in 1917 and an account of it was prepared for publication, but, so far as known to the writers, it has not yet appeared in print.

More recently it has not been considered necessary to maintain the existing pressure, but only to prevent a great reduction of pressure. Accordingly, about a pint of fluid has been withdrawn before starting to put in any oxygen, and after that simultaneous replacement was carried out volume for volume until the oxygen began to come away through the aspirating needle.

The last three observations in Table VII are from the same case and show a gradual increase of negative pressure after oxygen replacement. They indicate gradual absorption of the oxygen.

Table VIII affords a convenient comparison of average mean pressures and average excursions from the summaries of Tables I to V.

#### *Conclusions.*

Owing to the errors of the method of measurement above described and to an insufficient number of observations the conclusions are put forward tentatively and not as proved facts.

1. Fluid or air in the pleural cavity reduces the normal negative pressure and may convert it into a positive pressure.



2. The degree of reduction of intrathoracic pressure depends on the volume of fluid or of air or of both in the cavity.

3. Small haemothoraces do not give positive mean pressures. Large haemothoraces or haemopneumothoraces may do so.

4. The pressure in a sterile haemothorax changes little during the first sixteen days after wounding.

5. The respiratory excursion of pressure in small haemothoraces increases gradually during the first sixteen days after wounding.

6. The respiratory excursion in large haemothoraces is less than in small ones.

The excursion seems to be greater when there is air in the pleural cavity than when there is fluid only.

8. Pressures observed in pleural effusions were similar to those in haemothorax.

9. By simultaneous replacement of fluid withdrawn by oxygen volume for volume, existing pressure in the pleural cavity can be maintained.

TABLE I.

*Small Haemothoraces: Sterile.*

1st week after wounding.						
Obs. No.	Day.	Insp.	Exp.	Mean.	Excurs.	Other notes.
1	3	—	—	-6	—	Same case as No. 5 below
2	4	-10	-8	-9	2	
3	4	—	—	-6	—	
4	5	-5	-4	-4.5	1	Asp. 300 c.c. on 5th day
5	6	-8	-4	-6	4	
2nd week.						
6	6	-13	-4	-8.5	9	Asp. 300 c.c. 9th day
7	8	—	—	-6	—	
8	9	—	—	-6	—	
{ 9 Lt.	10	-9	-8	-7.5	1	Bilateral haemothorax
{ 10 Rt.	10	-9	-7	-8	2	Same case as No. 12 below
11	11	-6	at	-3	6	Asp. 400 c.c. 11th day
3rd week.						
12 Rt.	16	-10	-2	-6	8	Asp. 450 c.c. 16th day. See No. 10 above
13	16	-8	at	-4	8	

*Summary of Table I.*

	1st week.	2nd week.	3rd week.	Average mean.
Average mean pressure	-6.26	-6.5	-5	-6.2
Excursion average	2.1	4.5	8	4.5

TABLE II.

*Moderate or Large Haemothoraces: Sterile.*

1st Week.							
No.	Day.	Insp.	Exp.	Mean.	Excurs.	Size.	Other notes.
14	1	-3	-1	-2	2	Mod.	Asp. 165 1st day
15	4	—	—	+4	—	Large	Asp. 800 c.c. 4th day. Not emptied
16*	5	—	—	+2	—	Mod.	Asp. 300 c.c. 3rd day at C.C.S. Asp. 750 c.c. 5th day at Base
2nd Week.							
17	8	—	—	-8	—	Mod.	Same case as No. 20 below
18	8	—	—	-4	—	Mod.	Asp. 500 c.c. 8th day
19*	9	-6	-2	-4	4	Mod.	Asp. 500 c.c. ? date at C.C.S. Asp. 800 c.c. 9th day at Base
20	11	-6	-4	-5	2	Mod.	Asp. 500 c.c. 11th day
3rd Week.							
21	16	—	—	at	—	Mod.	Asp. 780 c.c. 16th day
22	17	at	+3	+1.5	3	Large	Asp. 1,700 c.c. 17th day
23	19	—	—	-7	—	Mod.	Asp. 700 c.c. subsequently
24	23	—	—	-2	—	Mod.	

*Summary.*

Average mean pressure . . . . .	= -2.5
Excursion average . . . . .	= 2.4

\* These cases having been aspirated before the observation of pressure was taken are excluded from the combined averages.

TABLE III.

*Infected Haemothoraces.*

No.	Days.	Insp.	Exp.	Mean.	Excur.	Size.	Other notes.
25	8	-5	-2	-3.5	3	Small	B. coli
26†	8	-1	at	-0.5	1	?	Asp. at C.C.S. Date ? B. coli
27*	3	-5	-3	-4	2	Mod.	Sterile. Same case as 28
28	13	-1	-0.5	-0.75	0.5	? Large	Gas-forming bacillus
13*	16	-8	at	-4	8	Small	Sterile. Taken from Table I
29*	18	-1	+1	at	2	? Larger	Sterile. Same case as 13 and 30
30	23	-8	-2	-5	6	?	Short-chained strep.

*Summary.*

Average mean pressure . . . . .	-3.08
Excursion average . . . . .	3.17

\* These observations having been associated with no proof of infection at the time are not included in the summary.

† Not included in summary because of previous aspiration.

TABLE IV.

*Pneumothoraces: Traumatic.*

No.	Days.	In air or fluid.	Insp.	Exp.	Mean.	Excur.	Size.	Other notes.
31*	5	Air	-2	+6	+2	8	Large	Much air withdrawn and later 850 c.c. clear fluid
32	7	Air	-12	-2	-7	10	Small	Contusion with fract. ribs
33	9	Air	-13	-6	-9.5	7	Small	Contusion with fract. ribs
34† Lt.	8	Pl. cav.	-14	at	-7	14	Nil	Same case as 35. Ex- plor. asp. yielded no- thing
35 Rt.	8	Fluid	-8	+8	at	16	Mod.	Asp. 200 c.c. and air 11th day
36	9	Fluid	-4	+4	at	8	Mod.	Same case as 37
37	12	Fluid?	-8	at	-4	8	Mod.	Asp. 160 c.c. and air
38	8	Fluid	—	—	-2	—	? Mod.	Same case as 39
39	16	Air	-8	+4	-2	12	? Mod.	
40	12	Air	-7	at	-3.5	7	Large	Same case as 41 and 42
41	12	Fluid	-8	-6	-7	2	Large	
42	16	Fluid	-2	+3	+0.5	5	Large	Asp. 800 c.c. and air

*Summary.*

Average mean pressure	. . . . .	-3.4
Excursion average	. . . . .	8.3

\* Infected with strep. and staph. The rest were sterile.

† An example of pressure in an apparently normal pleural cavity. Observations 31 and 34 are excluded from the summary.

TABLE V.

*Pleural Effusion: Non-Traumatic.*

Before Aspiration.							After Aspiration.						
No.	Date.	Insp.	Exp.	Mean.	Exc.	Asp.	Date.	Insp.	Exp.	Mean.	Exc.	Reduct.	
43	?	—	—	+6	—								
44	15/7	-18	-4	-11	14								
45	2/7	-4	-2	-3	2								
46	7/7	-8	-4	-6	4								
47	?	—	—	+1	—	4 pts.	Same	—	—	-13	—	14	
48	15/7	-12	-2	-7	10	? Amount	15/7	-14	-4	-9	10	2	
49	17/7	-8	-1	-4.5	7	? Amount	17/7	-18	-4	-11	14	6.5	
50	2/7	-6	-3	-4.5	3	1,000 c.c.	2/7	-16	-14	-15	2	11.5	
51*	—	—	—	—	—	—	9/7	-12	-4	-8	8	3.5	
52	5/7	-6	at	-3	6	600 c.c.	—	—	—	—	—	—	
53*	—	—	—	—	—	—	9/7	-14	-4	-9	10	6	

*Summary.*

Average mean pressure.	Before asp.	. . . . .	-4	After	. . . . .	-12
Excursion average.	Before asp.	. . . . .	7	After	. . . . .	8.7
Average mean pressure of all cases before asp.	. . . . .	. . . . .	. . . . .	. . . . .	. . . . .	-3.5
Excursion average of all cases before asp.	. . . . .	. . . . .	. . . . .	. . . . .	. . . . .	5.7

\* Not included in average because observed several days after aspiration.

TABLE VI.  
*Effects of Aspiration on Pressure.*

Haemothoraces.														
Before.								After.						
No.	Day.	In air or in fluid.	Insp.	Exp.	Mean.	Exc.	Asp. c.c.	Day.	In air or in fluid.	Insp.	Exp.	Mean.	Exc.	Reduct.
54	5	?	at	+2	-1	2	300	5	?	3	at	-1.5	3	2.5
8	9	?	—	-6	-6	—	300	9	?	—	—	-8	—	2
18	8	?	—	—	-4	—	500	8	?	—	—	-8	—	4
16	5	?	—	—	+2	—	750	5	?	—	—	-12	—	14
21	16	?	—	—	at	—	780	16	?	—	—	-12	—	12

Haemopneumothoraces.														
37	12	Fluid	-8	at	-4	8	160 + air	12	Fluid	-22	-12	-17	10	13
55	10	Fluid	—	—	+1	—	350	10	Fluid	—	—	-4	—	5
42	16	Fluid	-2	+3	+0.5	5	800 + air	16	Fluid	-14	-2	-8	12	7.5
35	8	Fluid	-8	+8	at	16	—	—	—	—	—	—	—	—
36	—	—	—	—	—	—	200 + air	11	?	-14	-6	-10	8	10

TABLE VII.

## Haemothoraces Replaced with Oxygen.

Before.								After.							
No.	Day.	In air or in fluid.	Insp.	Exp.	Mean.	Exc.	Asp. c.c.	O <sub>2</sub> put in c.c.	Day.	In O <sub>2</sub> or fluid.	Insp.	Exp.	Mean.	Exc.	Reduct.
20	11	?	-6	-4	-5	2	500	400	11	?	-6	-4	-5	2	0
11	11	?	-6	at	-3	6	400	q.s.	11	?	-5	at	-2.5	5	-0.5
22*	17	Fluid	at	+3	+1.5	3	1,700	1,600	17	?	—	—	+2	—	+0.5
57	20	—	—	—	—	—	—	—	20	O <sub>2</sub>	-8	+6	-1	14	-2.5
58	25	Fluid	-6	-3	-4.5	3	300	Nil	25	O <sub>2</sub>	-14	at	-7	14	-2
							+ O <sub>2</sub>								

\* Observations 22, 57, and 58 were made on the same case on different days.

TABLE VIII.

Table No.	Average Mean.	Excursion Average.	Group.
1	-6.2	4.5	Small haemothorax, sterile
2	-2.5	2.4	Moderate or large haemothorax, sterile
3	-3.08	3.17	Haemothorax infected
4	-3.4	8.3	Pneumothorax
5	-3.5	5.7	Pleural effusion

DIAGRAM I.

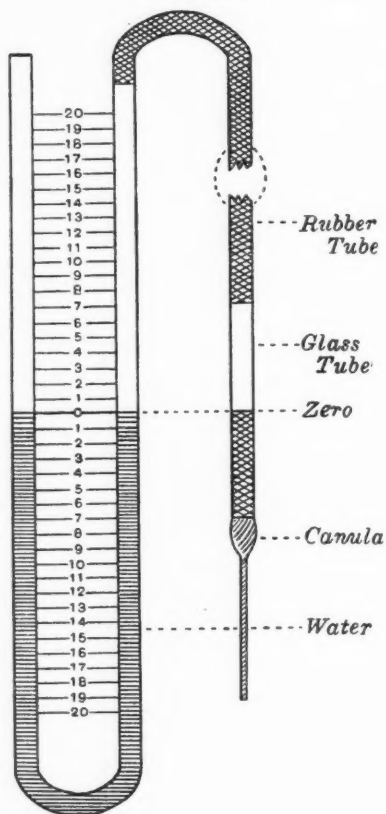
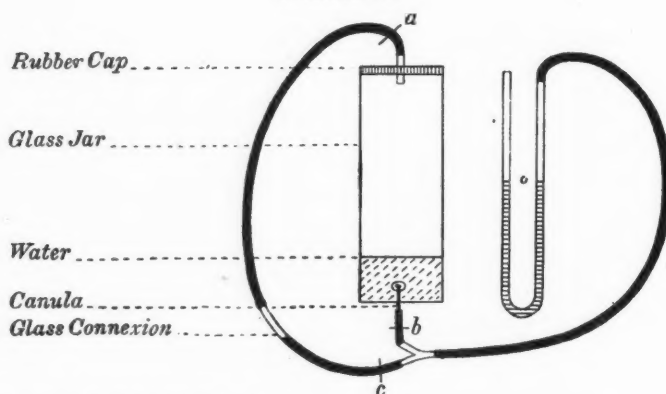


DIAGRAM II.



NOTE.—(1) *a*, *b*, and *c* are clamps.

(2) The glass connexion is easily detachable and is connected with pump or bulb for obtaining positive or negative pressures.

# A CONTRIBUTION TO THE STUDY OF CONTRALATERAL SIGNS IN GUNSHOT WOUNDS AND INJURIES OF THE CHEST

By S. W. CURL

## *Introduction.*

WHEN first taking up the study of gunshot wounds of the chest I was forcibly impressed by the apparent great frequency with which, in the case of injury to one side, abnormal signs were to be found on the uninjured side, and although further experience has led me to conclude that such signs are not so frequent as I had at first anticipated, yet they are, I believe, far more frequently met with in war injuries than in chest affections in civil life. The cases on which this paper is based are those which have come under my notice at a Base Hospital in France.

If we accept the definition in its widest sense, the appearance of contralateral signs in pulmonary or pleural affections is nothing new, and although, I believe, more common in cases of chest wounds and injuries received in action, yet similar, if not identical, signs are not uncommonly found in cases of pulmonary or pleural affections met with in civil life. For example, in acute pulmonary affections, e.g. pneumonia, a temporary compensatory emphysema of the uninvolved part of the lung or of the opposite lung takes place, and may be recognized by a hyper-resonance of the region occupied by the emphysematous lung coupled with a puerile type of breathing. In chronic pulmonary affections, where considerable areas of the lung are either rendered functionless or destroyed as a result of fibrosis, the uninvolved parts of the lung or the healthy lung undergo permanent compensatory changes and give rise to a puerile or exaggerated type of breathing. A third type of contralateral signs which may occur in pulmonary disease is that met with as a result of failing cardiac power where moist râles, the result of oedema, are audible over the 'healthy' lung.

In pleural affections one meets with two main forms of contralateral signs. In large effusions where marked embarrassment of the pulmonary circulation exists, or when the heart is failing, a congested and oedematous condition of the opposite lung sets in, as indicated by the appearance of numerous moist râles. In even moderate-sized pleural effusions an area of impaired resonance or of dullness may appear at the back of the opposite lung and take on the characters of the so-called Grocco's line of paravertebral dullness. The method of production of this is by no means certain; some consider it the result of an actual



displacement of the mediastinum to the healthy side, whilst another view is that the pressure of the effusion limits the vibrations of the vertebrae and adjacent heads of the ribs on the healthy side (1).

One may conveniently group the cases presenting contralateral signs as follows:

1. Those with contralateral pleurisy.
2. Those with contralateral pneumonia.
3. Those in which no clear evidence of pneumonia exists and in which the presence of râles forms the chief, if not the sole, contralateral sign.
4. Those in which the physical signs suggest a condition of consolidation or condensation of lung tissue and do not conform to any of the preceding conditions.

Up to the early part of this year my series of cases totalled sixty, and in twenty-nine of these contralateral signs of one kind or another were found, composed as follows:

Pleurisy in four cases.

Pneumonia in four cases.

Râles in seven cases.

Signs suggesting pulmonary consolidation or condensation, with or without the presence of râles in fourteen cases.

#### 1. *Contralateral Pleurisy.*

Signs of pleurisy on the contralateral side may be associated with pneumonia or broncho-pneumonia of the underlying lung, or they may occur quite independently. Of haemothorax cases pleurisy occurs most commonly in those that are infected, and especially so in streptococcal cases, and it may result in a sero-fibrinous or purulent effusion (2). In my cases pleurisy alone was found in three only, two being cases of infected haemothorax (Cases II and III) and one (Case I) a patient in whom there was a large foul-smelling wound leading down to the lung, the result of an attempt to remove a foreign body from the pulmonary tissue. In a fourth case (Case XXIX) contralateral pleurisy occurred consequent on a wound of the lumbar region of the opposite side, the lung on the stricken side being entirely unaffected. In this case a small quantity of blood-stained sero-fibrinous effusion was obtained from the contralateral side.

#### 2. *Contralateral Pneumonia.*

Pneumonia of the contralateral lung forms an interesting complication in the class of case we are considering. The chief interest pertaining to this condition lies in the great difficulty one frequently has in deciding whether or not the physical signs present are really dependent upon an inflammatory process,

inasmuch as the physical signs of pneumonia and of pulmonary collapse may be almost, if not quite, identical.

In endeavouring to form a just estimate of the probable condition of the underlying lung, it is necessary to take into consideration the associated signs and symptoms presented by the patient, especially noting the mode of onset, the temperature, the pulse and respiration rates, the character of the sputum, and the mode of evolution and involution of the signs. It may be here emphasized that blood-stained or blood-tinged sputum is *per se* no evidence of pneumonia, but a rusty viscid sputum is pathognomonic of inflammation of the lung. It must further be remembered that a rigor with sudden access of fever, coupled with increased frequency of pulse and respiration rates, even when associated with signs suggesting pulmonary consolidation (dullness and tubular breathing), are by no means always sufficient evidence for the diagnosis of pneumonia, as identical symptoms and signs may occur in cases of infected haemothorax, in which infected blood clot has been disintegrated and a generalized pleural infection has taken place.

It has been stated that much help is to be obtained in differentiating contralateral pneumonia from collapse by noting the position of the apex beat—in the former its position being practically undisturbed, whereas in the latter it is displaced to the contralateral side. Undoubtedly in those cases where one side of the chest is normal the position of the apex beat is of the greatest importance in helping one to a decision. In cases, however, where there is a collection of gas or fluid or both on one side of the chest and signs of consolidation or collapse on the opposite side, the evidence afforded by the position of the apex beat may be equivocal. In such cases it is obviously impossible to decide whether or not the displacement of the apex beat is the result wholly of the pleural effusion, or whether it in part depends on traction exerted by collapse of the opposite lung.

Under whatever circumstances it occurs, pneumonia must necessarily gravely modify the prognosis, and in cases of infected haemothorax is often the direct cause of death. Usually it appears to be of the broncho-pneumonic type, and one should be on the look-out for it in all cases of gunshot wound or other injury to the chest. Lobar pneumonia has been in my experience distinctly rare. In my series of cases contralateral pneumonia appeared in four (Cases IV, XIV, XV, XVI), in two of which (Cases IV and XVI) it was the direct cause of death.

##### 5. *Contralateral Râles.*

In some cases the sole or main contralateral sign is the presence of râles heard chiefly over the lower and posterior portions of the corresponding lung. Sometimes a unilateral bronchitis exists on the contralateral side, its presence being shown by the appearance of rhonchus or sibilus. More commonly, however, the character of the râles points to an implication of the finer air tubes or of the pulmonary parenchyma. I think it must be admitted that it is often

extremely difficult, if not impossible, to deduce the underlying condition of the lung from the character of the râles heard. With hypostasis and oedema, which are common, the mucous type of râle heard at the basal portions of the lung behind is the predominant adventitious sound, but crepitation may also be heard under these conditions. With collapse and patchy consolidation crepitant râles possessing a consonating character may be heard, and as oedema, collapse, and small areas of consolidation are not infrequently present in association, the character of the râles heard varies accordingly. More help is, I think, to be obtained by a general survey of the patient's condition and the circumstances under which the abnormal pulmonary signs appear. Of course, where the above-mentioned pulmonary changes are sufficiently marked, other signs than râles make their appearance, e. g. changes in the character of the breath sounds and an alteration in percussion note. Contralateral râles were present in Cases V, VI, XIII, XVII, XVIII, XIX, and XXVII.

#### *4. Signs suggesting the Presence of Contralateral Pulmonary Consolidation or Condensation.*

This group of cases is by far the most interesting of those showing contralateral signs, not only from the relative frequency with which signs of this character are found, but also on account of the considerable diversity of opinion as to their methods of production. In this group are included Cases VII-XII, XX-XXVI, and XXVIII. The physical signs presented by this group of cases vary somewhat, but conform mostly either to an increased or a diminished conducting power of the lung. In those cases where the conducting power of the lung is increased one finds in the slighter cases an alteration in the character of the breath sounds, indicated by the presence of broncho-vesicular breathing in the region of the angle of the scapula on the contralateral side. In more marked cases one finds typical bronchial or tubular breathing together with bronchophony, and in some cases most characteristic aegophony. Still more marked cases will show an impairment of the percussion note.

As already stated, these signs are most commonly observed not at the extreme base of the lung, but higher up in the neighbourhood of the angle of the scapula when the patient is sitting up with the arms a little forward. Sometimes the area over which these signs are to be detected is considerably more extensive, but the essential changes remain the same. Diminished conducting power of the lung is shown by the impairment of the percussion note, feeble or absent vocal fremitus, and feeble or absent breath sounds. In contradistinction to the former signs these latter are to be observed at the extreme base of the lung, although the area of their extension upwards may be considerable.

In extreme cases, in addition to the signs of one or other type described above, others are associated—flattening and shrinking of the parietes on the contralateral side together with the displacement of the heart, which may be extreme. Such cases as these can obviously be due only to extensive pulmonary

collapse. In the less marked cases, however, the explanation is by no means so obvious.

In those cases where bronchial breathing is present, pneumonia may be suspected, and indeed contralateral pneumonia is not infrequently the diagnosis made. In the majority of cases, however, this condition can be excluded with a considerable degree of probability. These signs occur frequently in patients who show nothing whatever to suggest an inflammatory condition of the lung. There may be next to no cough or expectoration and no more marked acceleration of the pulse-rate or respiration than can be fully explained by the general condition of the patient; there may be no fever. Further, the absence of any definite alteration in the physical signs for days together, and often the entire absence of râles, are confirmatory evidence of the absence of any inflammation of the lung.

It has been suggested that the physical signs are merely those of a hypostatic congestion and oedema of the posterior parts of the lung, such as may frequently be observed where deficient cardiac power and prolonged recumbency are obtained. Undoubtedly, in a large number of chest wounds and injuries, factors are present which tend to the production of hypostasis, such as cold, exhaustion, shock, loss of blood, &c., but such an explanation is, I believe, inadequate, inasmuch as râles are often entirely wanting, whereas in stasis râles may be said to be the dominant physical sign. Aspiration of blood into the bronchi of the contralateral lung and the subsequent production of patches of broncho-pneumonia has been put forward to explain the presence of those contralateral signs. Here again the explanation is inadequate, as it is almost impossible to conceive of a condition of broncho-pneumonia existing in which râles are entirely absent. Probably the view that has the largest number of supporters is that the signs observed are those resulting from pulmonary collapse, and although, as I shall endeavour to show, collapse is not the sole cause, yet there appears good reason for thinking that it is probably a common occurrence.

The physical signs presented accord well with those found in pulmonary collapse. A moderate degree of collapse in which the bronchi are still patent should on theoretical grounds give rise to the signs which are actually observed, namely, broncho-vesicular or bronchial breathing with bronchophony, and if sufficiently marked an impairment of the percussion note. With greater collapse and stenosis or occlusion of the bronchi leading to the collapsed area one would expect a feebleness of vocal fremitus and of breath sounds going on to an entire absence of these, coupled with dullness on percussion. The frequent entire absence of râles is further evidence in support of the theory of collapse.

In the extreme cases, where, with a contraction of the contralateral side, the heart is drawn over to the same side, pulmonary collapse, of course, must exist to a marked degree. An absence, however, of any appreciable displacement of the heart's apex is, I think, no evidence that pulmonary collapse does not exist. I have seen pulmonary collapse on the contralateral side in the postmortem

room where the collapsed area extended only for about one-third of an inch deep to the pleura, and it is reasonable to assume that small areas of collapse such as this, although insufficient to give rise to any appreciable alteration in the position of the heart's apex beat, yet would suffice to give rise to the abnormal physical signs such as are at times to be found.

If pulmonary collapse be one of the conditions giving rise to the contralateral signs which we are now considering, how is it brought about? Of the various suggestions that have been put forward in explanation two especially merit attention, namely, bronchial obstruction and diaphragmatic paralysis. It has been suggested that the pulmonary collapse is the result of a plugging of the bronchi with retained secretion, much in the same way that collapse occurs in association with broncho-pneumonia.

A large number of cases of gunshot injuries of the chest undoubtedly show a catarrh of the respiratory passages, and in some cases this catarrh appears to be almost, if not entirely, limited to the contralateral lung. For these reasons it has been argued that the pulmonary collapse is the result of bronchial obstructions. It appears highly probable that in some cases, especially the slighter ones, obstruction of the smaller bronchi with secretion may be one of the contributing factors in the production of collapse. In those cases where the area of collapsed lung is considerable there are clinical grounds strengthening this supposition. But it may well be argued that the existence of a bronchial catarrh with a collapsed lung is no evidence that the latter is the result of the former. The mechanical defects of a collapsed lung would obviously lead to the stagnation of secretion and favour its subsequent infection. Lastly, these contralateral signs may be present with the entire absence of a respiratory catarrh.

A reflex paralysis of the diaphragm has been suggested as a possible explanation in at least some of these cases (3). It has long been known that paralysis of the diaphragm may give rise to a massive collapse of the lung (4), and, as the authors of the preceding paper have suggested, this may in some cases be the explanation of contralateral collapse.

My early experience of war injuries of the chest had given me the impression that in those cases where contralateral signs, such as we are now considering, were present, these were dependent upon the existence of a pulmonary collapse, pure and simple, except in those relative rare examples in which a bilateral haemothorax existed. Further experience, however, and exploratory puncture of the contralateral side in several cases recently have shown me that, apart from blood effusion, other exudates on the contralateral side may exist and, in association doubtless with coexisting pulmonary collapse, give rise to signs suggesting consolidation. To illustrate this fact the following cases may be quoted:

A., aged 42. Wounded low down at the back of the left chest May 21, 1918. Admitted into hospital May 25, presenting on the following day the signs quoted below:

Somewhat impaired note with weak breath sounds in the left axilla. At



the right base behind there were impaired note, faint bronchial breathing, and crepitations. The apex beat was in the normal position.

*Diagnosis.* Slight collapse of left lung and a pleural effusion at the right base.

X-rays on May 26 confirmed the presence of an effusion at the right base. No F. B.'s were seen in the chest. The same day the right base was explored and a syringe of turbid serum was withdrawn. The fluid contained numerous polynuclear cells, but was sterile.

B., aged 18. Wounded by shrapnel in the third right interspace, close to sternum, May 7, 1918. Admitted to hospital May 18, presenting the following physical signs:

Dullness on percussion at 9th right rib behind with feeble breath sounds below. Below angle of left scapula there were impaired note, broncho-vesicular breathing, and crepitations.

*Diagnosis.* Small haemothorax at the right base and collapse of left lower lobe. X-rayed May 19. No F. B. seen in chest. Right lung appears clear. Left lower lobe appears collapsed. Heart slightly to left.

May 30. Left base explored. Syringe of turbid serum containing a large lymph plug obtained. This pleural fluid clotted completely, contained flakes of lymph and many polymorphs in flakes. No endothelial cells were seen, and cultures for twenty-four hours were sterile.

C., aged 34. Wounded by shrapnel over left shoulder, April 11, 1918. Admitted to hospital April 13, presenting the following physical signs:

The left chest in front was hyper-resonant and there was some surgical emphysema about the left scapula. The apex beat was one finger's breadth to the left of the nipple line. At the left base behind the percussion note was slightly impaired, but breath sounds and vocal fremitus were present. At the right base behind there were dullness, broncho-vesicular breathing, and a small patch of bronchophony.

On April 17 the wound was opened up and the subspinous plate of the scapula was found to be perforated near the angle. A second incision was made over the 7th rib and a F. B. removed. At the time of operation the right base was explored and some bright red blood-stained pleuritic fluid was removed. This contained tissue cells in large numbers but no polymorphs, and was sterile both by film and culture.

D., Case XXIX in Appendix. In this case there was marked collapse of the contralateral lung, and a pleural effusion on this side. The 'injured' side of the trunk beyond surface wounds in the right loin showed no abnormality. The pleural fluid (100 c.c.) removed by aspiration contained endothelial cells in large numbers and very few polynuclears, and no evidence of infection was found.

In none of these four cases was there any evidence to suggest that foreign metallic particles had perforated or entered the contralateral side of the chest, and examination by the X-rays confirmed this view. In Cases A, B, and C, the contralateral signs were such as to suggest the presence of solid lung, whilst in D the presence of the pleural exudate would have been missed had it not been for the occurrence of pleural friction over the front.

The chief points noticeable in the characters of the fluid obtained by puncture are:

1. Its sterility in all four cases.
2. The presence of endothelial cells in numbers (Case B excepted).
3. The complete absence or scarcity of polynuclear cells. Case B was an



exception, but here the numerous polynuclears may have been largely derived from a 'lymph' plug which was sucked into the syringe at the time of exploration.

These facts suggest that the outpouring of exudate on the contralateral side was the result, not of a microbial infection of the pleura, but of a mechanical irritation of this endothelial membrane. The probable cause of such irritation was a bruising of the surface of the lung by the chest-wall from contre-coup, entirely analagous to the condition seen in head injuries, where the cortex or meninges of one side may be damaged as a result of a blow on the opposite side of the skull.

#### *Conclusions.*

My experience of gunshot wounds and other injuries of the chest met with in warfare has led me to the following conclusions :

1. That contralateral signs are common.
2. That contralateral collapse is quite common, and that its causes are probably manifold.
3. That the combination of physical signs supposed to be characteristic of solid lung is extremely fallacious and uncertain, since fluid effusions may give rise to identical signs.
4. That examination of cases by X-rays, although extremely helpful, is by no means sufficient for the differentiation of solid lung from pleural effusions.
5. That in the differentiation of solid lung from pleural exudates the only safe guide is the use of the exploring needle, and that even the use of this may fail unless exercised with discretion.
6. That with a pleural exudate the heart is generally displaced to the opposite side, but in a small percentage of cases a fluid exudate may exist on the side to which the heart is displaced, doubtless owing to the concomitant presence of marked pulmonary collapse.
7. That one at least of the causes of contralateral signs simulating solid lung is the presence on the contralateral side of a pleural exudate, and that this exudate results from a bruising of the pleura produced by the method of contre-coup.

#### *Appendix of Cases.*

*Case I.* Aged 40. Shrapnel wound of right lower chest at the back, September 19, 1917. At C. C. S. attempt made to remove F. B. from right lung. Admitted October 6, looking thin and ill with slight fever. A large foul-smelling wound over back of right chest, exposing the lung substance. Much cleaning up and closing in of wound after a week's treatment. Developed dry pleurisy over left side a few days after admission.

*Case II.* Aged 31. Wounded by rifle bullet below outer end of right clavicle, September 20, 1917. Admitted October 21, and was at first thought to have pneumonia and was desperately ill. October 1, 100 c.c. of thin blood-stained fluid were aspirated from the right pleural cavity; fluid sterile. October 23, two pints of thin pus were removed by aspiration and film preparations showed streptococci. Rib resection, October 23—tube and drainage. Steady but slow improvement thenceforth. Irrigation of cavity with eusol. Developed dry pleurisy of the left side and on the right a broncho-cutaneous fistula. Ultimately made a good recovery.

*Case III.* Aged 21. Shell wound of right lower axilla splintering 8th rib, October 12, 1917, and leaving a large gaping wound. Admitted October 13, looking very ill. Temperature 103°, pulse 108, and respirations 24. Small right haemothorax. October 15, one ounce of bright red blood was aspirated from right chest; fluid sterile. October 22, splintered rib trimmed; a small quantity of blood-stained fluid was removed from right pleural cavity; fluid grew a diphtheroid. After continued high temperature for several days, began to mend and was convalescent by first week of December. About December 7, developed dry pleurisy of left side. Sent to England some days later in good general condition.

*Case IV.* Aged 21. Multiple wounds, November 17, 1917, right loin, back of right shoulder, left side of abdomen. At C. C. S. wound of right loin found to penetrate chest and rib fractured. Rib excised, B. I. P. dressing, closed. Admitted November 25. Right pneumothorax with some fluid. Explored November 25; film and culture sterile. December 5, signs of broncho-pneumonia with pleurisy at left base. Right chest explored, December 6; dark, bloody fluid containing non-encapsulated diplococci. Rib resection and drainage. Broncho-pneumonia extended and patient died December 14.

*Post-mortem.* Right pleural cavity empty of fluid. Pleura covered with lymph; lung partly collapsed. Left lung riddled with broncho-pneumonia: some dry pleurisy. Slight atheroma of aorta; recent pericarditis and recent infarcts of spleen. White infarct in right kidney.

*Case V.* Aged 26. Shrapnel wound below angle of left scapula, October 12, 1917. Admitted October 17. October 18, signs were as follows: Dullness at left back from the 8th space to the base, with feeble vocal fremitus and vocal resonance and absent breath sounds. Crackling râles were present at the right base behind. Diagnosis—Left haemothorax.

*Case VI.* Aged 25. Two wounds (bomb) right chest low down at the back, November 13, 1917. November 14, right chest explored—also on 18th and 21st. Anaerobes on each occasion. Admitted to hospital December 4. Signs of right pneumothorax with some fluid. Looked ill and septic. Right chest explored and some bloody pus containing streptococci removed. *B. coli* and diphtheroids were also present in the fluid. Resection 8th rib; escape of free gas and much chocolate-coloured fluid. Washed out with saline-tube. December 5, escape of bile-stained fluid from tube and tiny particles of liver substance. A few râles appeared over base of left lung the day after operation; these soon disappeared. Steady convalescence.

*Case VII.* Aged 25. Wounded October 9, 1917, below left clavicle and near spine of left scapula, ? missile. Had a left-sided pneumothorax. At C. C. S. wounds were excised and stitched. Admitted to hospital October 12, 1917. The following day physical signs suggesting pulmonary collapse were present on the left side, e.g. impaired percussion note from middle of scapula to base, with weak vocal fremitus, bronchial breathing, and some agophony. At

the right base behind there were impaired resonance, bronchial breathing, and bronchophony. Made a good recovery.

*Case VIII.* Aged 23. Shrapnel wound over spine of right scapula, October 2, 1917. Admitted to hospital October 4. Right chest explored, October 6, as physical signs suggested fluid. Dullness from angle of scapula to base, with vocal fremitus just present, absent breath sounds and absent vocal resonance. No fluid obtained by exploration; ?pulmonary collapse. At the left base behind there were dullness on percussion and weak breath sounds. X-rays showed obscurity of the lower part of the right chest, also two small F. B.'s and fracture of 1st and 2nd right ribs at the back. Made a good recovery.

*Case IX.* Aged 37. Shrapnel wound below the right clavicle, October 1, 1917. Admitted to hospital October 2. On the following day examination revealed physical signs of right haemothorax, e.g. dullness from 7th right rib behind to base with absent breath sounds. The heart was displaced to the left. At the left base behind there was bronchial breathing.

*Case X.* Aged 21. Shrapnel wound lower part of left back, October 31, 1917. On November 8, the day after admission to hospital, there were the signs of a left haemothorax. At the right base behind there were broncho-vesicular breathing and bronchophony. Left chest aspirated November 8, 1,000 c.c. of sterile bloody fluid being removed. Developed thrombosis of right saphena vein, November 16, from which he slowly recovered.

*Case XI.* Aged 30. Revolver bullet wound over lower end of right side of sternum, December 8, 1917. On December 18, the day after admission to hospital, there were the signs of a right haemothorax. About the angle of the left scapula there were broncho-vesicular breathing and bronchophony. December 19, 700 c.c., and December 20, 350 c.c., of sterile blood-stained fluid aspirated from right chest.

*Case XII.* Aged 23. Shrapnel wound right posterior axilla and through and through wounds upper arm, November 24. December 4, the day after admission to hospital, there were signs of a right haemothorax (small) from which small quantities of blood could be aspirated—cultures sterile. At the left base behind there were impaired percussion note, a few crepitations, and bronchial breathing from angle of scapula to base. On December 15 râles were no longer audible at the left base, otherwise the signs on this side were as before.

*Case XIII.* Aged 34. Shrapnel wound right chest, October 10, 1917, and of both buttocks. October 11, wounds of chest and buttocks opened up and drained. Admitted to hospital October 13, and 600 c.c. of dark blood containing streptococci were aspirated from the right chest. Same day 7th rib resected. Blood clot and large quantity of bloody fluid were evacuated. Swabbed out with saline-tube. Developed râles over lower half of left lung, with increased vocal fremitus and bronchophony. Severely toxic. Died December 18.

*Post-mortem.* Thin yellow pus coating on costal and visceral pleura of right chest—very little fluid. Right lung, on section, purple, non-crepitant, and sank in water. Patches of collapse in left lung and a few subpleural haemorrhages.

*Case XIV.* Aged 24. Contused rifle bullet wound of right axilla, October 10, 1917. October 13, at C. C. S. wound excised. Pleura not penetrated. Tissues in axilla sloughing; wound left open, B. I. P. dressing. Admitted October 15, with signs of fluid in right pleural cavity. At the left base behind there were dullness on percussion, diminished vocal fremitus, increased vocal resonance, faint bronchial breathing, and crepitations. The

sputum was blood-stained muco-pus. October 22, 100 c.c. of blood-stained pleuritic fluid were aspirated from right pleura, containing a small non-encapsulated diplococcus which aerobically grew freely. November 10, a small quantity of reddish-yellow fluid was aspirated from right chest growing a diplococcus. November 13, the only signs at the left base were broncho-vascular breathing and crepitations. X-ray on November 14 showed loss of translucency of the right chest, especially in the axillary region, and fracture of right 8th and 9th ribs, front and back. Right diaphragm moved very little, the left moved well. On November 15 the temperature had reached normal; on the 24th it rose to 102.6° and exploration of the right chest showed the presence of creamy pus. November 26, rib resection, about two ounces of pus evacuated—tube. Discharged about a fortnight later with a gauze drain in sinus, and in good general health.

*Case XV.* Aged 25. Bomb wound below angle of right scapula and of 2nd right space in front, October 10, 1917. Admitted to hospital October 12, with signs of right haemothorax. There was surgical emphysema over back and front of the chest, especially on the right side. On October 14 signs of broncho-pneumonia of the left lung had become very manifest. Right chest aspirated, October 12, 8 c.c., and October 14, 100 c.c., of bloody sterile fluid being obtained. Made very slow progress. November 29, some creamy blood-stained pus removed from right pleura—diplococcus. Same day resection of 8th right rib—cavity containing pus situated between base of lung and diaphragm and in the axillary region—tube. Thereafter good progress.

*Case XVI.* Aged 25. Contour bullet wound left axilla, October 2, 1917. At C. C. S. wound excised. Pleura penetrated. Pleura closed by approximating diaphragm. Partially sutured (October 4). Admitted to hospital October 7. Very ill, high intermittent temperature, pulse 108, respirations 32. Sputum, rusty muco-pus. Dull from 7th right rib behind to base, with diminished vocal fremitus, intense bronchial breathing, bronchophony, and crackles. Dull at left back from 8th rib to base, with diminished vocal fremitus, very faint breath sounds, and some crackles. Apex beat 5th left space in nipple line.

For six days temperature oscillated between 103.8° and 99.2°; October 13, it fell to normal, but rose to 103° next day. Patient gradually got worse and died October 17.

*Post-mortem.* Left chest full of slightly turbid fluid. A small pocket of pus in connexion with left pleura covering upper surface of diaphragm. Left lung very collapsed. No pericarditis. Right lung showed broncho-pneumonia of upper and middle lobes and lobar type of this in lower lobe.

*Case XVII.* Aged 22. Bomb wound below right clavicle and lower part of right chest at the back, October 14, 1917. Admitted to hospital October 26, with signs of right haemothorax. From angle of left scapula to base were heard consonating râles. No sputum. October 23 and November 8, 100 c.c. blood aspirated from right chest on each occasion; fluid sterile. Made a good recovery.

*Case XVIII.* Aged 20. Bruising of right lower chest by shell fragment, November 21, 1917. Urine full of blood the same day. Admitted to hospital December 2, with signs of small effusion at right base. Moist râles over left base behind; by the following day these had disappeared. December 12, a small quantity of blood-tinged fluid removed from right chest—contents endothelial cells—sterile. Made a good recovery.

*Case XIX.* Aged 33. Hit on right side of chest by piece of shell case. No wound. Admitted to hospital December 12, 1917, with signs of right pneumothorax with fluid. December 13, 1,000 c.c. of bloody fluid removed from right chest by aspiration. Gram-negative rod, ? *B. coli*. Crepitations scattered

over base of left lung. Right chest aspirated again, December 15, 250 c.c. bloody fluid removed. Did not improve. Rib resection, January 28: gas escaped. Parietal pleura thickened. Three pints of brownish-yellow pus evacuated containing cocci and *B. coli*. Lung absolutely collapsed. Diaphragm pushed down. Small tube.

*Case XX.* Aged 20. Shrapnel wound over outer part 4th left rib, October 12, 1917. October 15, 20 ounces of fluid removed from left chest. Admitted to hospital, October 17. Bronchial breathing, bronchophony, and crackles at left base behind and bronchial breathing and bronchophony at the right base.

*Case XXI.* Aged 35. Shrapnel wound over vertebral border of right scapula, September 16, 1917. Admitted to hospital September 21, with dullness at right base behind from 9th rib; ? small haemothorax. At left base behind bronchial breathing and bronchophony.

*Case XXII.* Aged 20. Shrapnel wound left interscapular space, October 4, 1917. On October 7 there were signs suggesting the presence of a left-sided haemothorax—impaired note from middle of scapula to base with absent vocal fremitus and weak breath sounds. The heart was displaced to the right. At the right base behind there were impaired percussion note, absent vocal fremitus, and weak breath sounds. Made a good recovery.

*Case XXIII.* Aged 25. Bomb wound left chest, September 29, 1917. At C. C. S., chest wound excised—found to be into lung—pleura sewn up. B. I. P. and suture. Admitted into hospital October 1. Next day physical signs were as follows: Dullness below angle of left scapula, with diminished vocal fremitus, increased vocal resonance, and very feeble breath sounds. Below angle of right scapula there were dullness and very feeble vocal fremitus. Sixteen days later there were impaired note and almost absent vesicular murmur at the right base behind.

*Case XXIV.* Aged 28. Shell wound of right shoulder, scalp, and right forearm, November 24, 1917. Admitted December 5, with signs of right haemothorax. Below angle of left scapula there were tubular character of expiration and an aegophonic tone of vocal resonance. Right chest aspirated, December 18, 1,000 c.c., and some days later 10 c.c., of bloody sterile fluid removed. Made a good recovery.

*Case XXV.* Aged 36. Shrapnel wound left shoulder region, October 4, 1917. Admitted to hospital October 8, with signs of effusion in left chest. Over right base behind there were impaired percussion note and crepitations. October 13, left chest aspirated; dark-coloured fluid containing encapsulated diplococci. October 14, resection of 7th left rib. Blood clot and fluid evacuated. Swabbed out with saline-tube. Improved very slowly.

*Case XXVI.* Aged 27. Shrapnel wound left mid-axilla, October 4, 1917. Admitted to hospital October 6, with signs suggesting fluid in left chest—heart much displaced to right. Over right lower chest behind bronchial breathing, bronchophony, and râles. Left chest explored several times without finding any definite pleural fluid. Was very ill and obviously getting worse. Explored again November 2, 1917, and 100 c.c. of sour-smelling chocolate-coloured fluid removed by aspiration—streptococci. The 8th and 9th left ribs were resected, 1½ pints of thin bloody fluid being evacuated. Washed out with saline-tube. Ultimately made a good recovery.

*Case XXVII.* Aged 25. Shrapnel wound over 8th right rib, posterior axillary line, also superficial wounds back of right thigh, right forearm, and left hand,



October 4, 1917. Admitted to hospital October 6, with signs of effusion in right pleura. At left base there was dullness below angle of scapula. October 7, 250 c.c. of dark blood were aspirated from right chest. The fluid contained coliform organisms and diphtheroids. October 12, 300 c.c. of fluid were again removed. The following day the 8th right rib was resected, bloody fluid and many clots being removed. Washed out with saline-tube. For many days after operation moist râles were present, together with impairment of percussion note over lower part of left lung. Some days after operation small particles of liver substance appeared on the dressings. Patient remained in a very grave condition for many days after the operation, but later began to improve, and left hospital about three months after being wounded in very good general condition.

*Case XXVIII.* Aged 36. Wounded left chest and back on April 11, 1918. At C. C. S. the notes made were 'Pen. Wd. Left Chest, Heart to left. General condition good'. On admission to hospital, April 13, the condition was as follows: There was a circular wound over the upper and outer part of the left scapula and about the lower left scapular region. There was surgical emphysema. The heart's apex beat was one finger's breadth to the left of the left nipple. There was hyper-resonance all over the left chest in front, breath sounds were good, and vocal fremitus was present. At the left base behind the note was very slightly impaired, but vocal fremitus was present. At the right base behind there were dullness, broncho-vesicular breath sounds, and a small patch of bronchophony. On April 17 wound opened up; subspinous plate of scapula perforated by missile near lower angle. Second incision over 7th rib. F.B. removed and injured tissues excised. Flavine pack-suture. Needle to right base withdrew some bright red blood-stained pleuritic fluid which contained excess of tissue cells; no polynuclears seen and no infection by film or culture.

*Case XXIX.* Aged 32. Gunshot wound of right loin, January 28, 1918. At C. C. S. large through and through wound of right chest excised along with track. Sewn up. February 6, apex beat  $1\frac{1}{2}$  inches to left of left nipple line. Percussion note over front of left chest good to 3rd rib; impaired in axilla and here vocal fremitus and vocal resonance were impaired. Pleural friction down to 3rd left rib in front and weak breath sounds below. At the left base impaired note to 8th rib and below this dullness. Weak breath sounds all over left back. No physical signs of abnormality in right chest. Patient was very breathless and was spitting up muco-pus. February 10, apex beat was now in the nipple line, and on the right side opposite the middle of the scapula there was aegophony. February 11, a syringeful of slightly blood-tinged fluid was removed from the left pleural cavity, and a day or two later about 100 cc. of similar fluid were removed by aspiration; fluid sterile. Was quite convalescent by second week in March.

#### REFERENCES.

1. Taylor, *The Practice of Medicine*, Lond., 10th edit., 582.
2. Bradford, Sir J. R., 'On Gunshot Injuries of the Chest', *Brit. Med. Journ.*, August 4, 1917, 141 et seq.
3. Soltain, A. B., and Alexander, J. B., 'On Gunshot Wounds of the Chest as seen at a Base Hospital in France', *Quart. Journ. Med.*, Oxford, 1917, x, 259 et seq.
4. Pasteur, W., *The Bradshaw Lecture*, Royal College of Physicians, 1908, 16.



## TWO CASES OF ENDOCARDITIS DUE TO *BACILLUS INFLUENZAE*

By ARCHIBALD MALLOCH AND LAWRENCE J. RHEA

DURING the twelve months ending December 1917, there occurred in a base hospital in France nine fatal cases of broncho-pneumonia from the lungs of which the influenza bacillus was recovered at autopsy. In all of these, save the first two, a clinical diagnosis of influenzal broncho-pneumonia was made before death. Three of these cases showed complicating lesions of the circulatory system; one a purulent pericarditis, and two an acute endocarditis due to the influenza bacillus. It is the purpose of this paper to place on record a description of these two latter cases.

Endocarditis occurring during the course of influenza has been reported in a considerable number of cases, but a closer examination of the question reveals two obvious sources of error in the use of the term 'influenzal endocarditis'. In the first place 'influenza' is a much-abused clinical term, and Mathers (9) has shown that in the epidemics to which that name is popularly applied, the catarrhal infection of the respiratory tract may be due very often to the streptococcus, pneumococcus, *Bacillus pneumoniae*, or staphylococcus, as well as to the influenza bacillus. Again, although the sputum in such cases may yield the influenza bacillus in predominating numbers, or in almost pure culture, this does not justify the assumption that lesions of the endocardium or arterial intima, occurring during the course of the disease, are to be ascribed to the same infection. In some such patients who have died the pneumococcus, streptococcus, staphylococcus, &c., have been isolated from the vegetations. To establish an absolute diagnosis the case must come to autopsy and the organism be recovered from the lesions; but the diagnosis is, of course, justified where the bacilli are repeatedly isolated from the blood in a case showing a clinically obvious, fresh endocarditis, continuing after the respiratory tract infection has subsided.

The fullest paper on endocarditis occurring during influenza is Lebreton's (5) Paris Thesis, and in this the author points out clearly the difficulties besetting the subject. He has collected from French, German, American, and English sources twenty-one instances of endocarditis occurring in cases where *B. influenzae* was obtained from the sputum or from blood culture, but in only three of

these cases was the bacillus found in smears or cultures from the vegetation as the only organism present. According to his judgement, nine more of the cases which he had collected might be truly called 'influenzal endocarditis', as the *B. influenzae*, although mixed with other bacteria, was isolated from the lesions in all of these. He makes the following statement regarding diagnosis of the condition: *Endocardite grippale* may occur early in the course of the malady, or as convalescence begins, and is much more frequent in adults than in children. The phenomena leading to suspicion of this complication include a rising temperature not accounted for by the condition of the lungs; palpitation, or pain and tenderness in the precordial region; chills. It may also be suspected when the blood-pressure, already low, falls still more; when a heart murmur appears, or when there is a change in a murmur already present. The endocarditis may be benign or malignant, and the former is the more frequent. The malignant form more commonly terminates in death, and is often complicated by pulmonary infarcts, or infarcts of the spleen, kidneys, or liver, or by arterial emboli which may cause local gangrene. Even paradoxical emboli may result.

Amongst the cases collected in his Paris Thesis, Lebreton cites two early ones reported by Jehle (4) in 1899. In the first of these there was acute endocarditis, and *B. influenzae* was recovered in pure culture from the vegetations. In the second case showing a similar lesion, culture showed staphylococcus as well as the influenza bacillus.

Horder (2), 1908, reports two cases of influenzal endocarditis (included in Lebreton's series); in one case on two, in the other on five separate occasions, *B. influenzae* was recovered in pure culture from the blood, and the diagnosis was thus made six and five weeks before death respectively. The first case showed at autopsy a growth on the left auricular wall which had ulcerated through the base of one of the aortic cusps. Blood culture at autopsy was sterile, possibly since the patient had been dead thirty hours; but smears and cultures from the vegetation showed the influenza bacillus alone. The lungs were clear, and the direct cause of death was cerebral embolism. In the other case, aged 13, the lesion was on the posterior aspect of the fused mitral cusps (site of old endocarditis). The heart's blood, *post mortem*, was sterile in this case also, but smears and cultures from the vegetations showed *B. influenzae* alone. Horder decided that the duration of the lesions in these cases was three and five months respectively, and that in each case the recent lesions were engrafted upon an endocardium already damaged by 'previous rheumatism'.

Marmorstein (8), 1908, reported two cases of aortitis occurring in patients suffering from influenza. In the first patient, aged 24, there was acute disease of the aortic cusps as well as of the intima of the aorta, but no cultural examination was recorded. In the second case, aged 22, death occurred one year after febrile infection, and autopsy revealed an aortitis, disease of the innominate artery, and thrombosis of the basilar artery, with emboli in the branches of the latter, giving rise to patches of suppurative encephalitis in the pons cerebri and

in the left hemisphere. Marmorstein, in this case, was able to recover the influenza bacillus from the brain, but not from the aorta.

Presslich (11) collected nine cases of endocarditis occurring in 'influenza', but only one of these cases was fatal. The mitral valve showed vegetations, but cultures were not made. Presslich's cases were all soldiers and all showed clinical evidence of 'la grippe'. The diagnosis of influenzal endocarditis was based on the finding of *B. influenzae* in the sputum, in some of the cases alone, in others mixed with other organisms.

Simons (13), 1914, in a critical review of bacterial endocarditis, collected from the literature 325 cases of the acute and chronic forms. Of these cases ninety-six were 'chronic endocarditis', of which ninety-two were caused by the *Streptococcus viridans*, and the remaining four by the influenza bacillus (diagnosis made before death by Libman). Also amongst the 325 cases Simon places six cases diagnosed clinically, and five diagnosed *post mortem* by Horder. It is not definitely stated, but we assume that these eleven cases were acute. Later, in discussing chronic endocarditis, Simons remarks, under the heading *B. influenzae*, 'not common, but never found except in chronic cases'. From the author's statistics we judge that he considers that the influenza bacillus may produce either acute or chronic lesions, but that in the latter case the lesion is always engrafted upon a previously diseased endocardium, and that primary acute endocarditis due to this organism does not lead to 'chronic endocarditis'. We are in doubt as to whether Simons includes under 'chronic endocarditis' those cases which in strict terminology should be classified as 'recurrent endocarditis' and 'healed endocarditis'. Referring to painful erythema (*nodosités cutanées éphémères*), Simons states that he has seen this only in cases of endocarditis due to the *Streptococcus viridans* or to the influenza bacillus.

Libman and Celler (6) report thirty-six cases of 'subacute infective endocarditis', in thirty-five of which blood cultures yielded atypical cocci, which are described, whilst the remaining case yielded *B. influenzae*. They state that in this latter case the clinical course and pathological findings were essentially the same as in the other thirty-five, and that even typical painful erythematous nodules were present.

*Case I. Summary. D. H., aged 39. Admitted third day of disease with diagnosis of bronchitis. Dyspnoea and pain in right side of chest; signs of consolidation of the right lung and of left base; diagnosed on sixth day as lobar pneumonia, but diagnosis changed on twelfth day to confluent influenzal broncho-pneumonia because of the finding of B. influenzae as the predominating organism in the sputum; examination of heart negative; temperature subnormal; very rapid respiration and pulse; heavy sweats; death on thirteenth day. Post-mortem examination: bilateral confluent broncho-pneumonia; dilated right heart, syphilitic aortitis also involving aortic ring; acute vegetative endocarditis of aortic cusps; mild chronic interstitial nephritis; B. influenzae grown in pure culture from terminal bronchioles, from heart's blood, and from vegetations on aortic cusps.*

*Full Case Report.*

D. H., aged 39, admitted from ambulance train March 7, 1917, with diagnosis of 'bronchitis'.

*Previous history.* The patient had served in the army in France for twenty-eight months. Since 1914 he had had three attacks of bronchitis. No other illness.

*Present illness.* He had been suffering from a 'cold' for about ten days, but his condition grew much worse two days before his arrival at the Base, pain in the right chest and difficulty in breathing developing, and the cough became more severe.

*Condition on admission (third day).* The patient was very dyspnoeic and could gain only comparative comfort by sitting propped up in bed. Examination of the heart showed nothing abnormal save an increased rate. The right side of the chest moved less than the left, and there was dullness in the right axilla, and posteriorly over the whole of the right lower lobe and the lower portion of the upper. The breath-sounds were distinctly blowing in character in the right axilla and over the area of dullness behind, and râles of all descriptions were heard. On the left side no dullness was made out, but many sibilant râles and moist crepitations were heard.

*Course of the disease (fifth day).* On the right side of the chest there was dullness over the front, axilla, and back, with blowing breathing throughout. Moist, sibilant, and sonorous râles were heard over both lungs. The condition was worse, and he was transferred to the ward for critical pneumonia cases.

*Sixth day.* Patient dyspnoeic and showing a moderate grade of cyanosis, no labial herpes. Tactile fremitus was increased over the right side. There was dullness over the whole of the right lung save at the anterior border, with blowing breathing and bronchophony throughout. Sibilant râles were heard over the anterior aspect of the right upper lobe, and 'crackles' in the right axilla. There was harsh breathing over the left upper lobe. Resonance was impaired over the lower left axilla, and here pleural friction sounds were heard, and distant blowing breathing. The pulse was full and regular. The sputum was slightly blood-stained.

*Seventh to ninth day.* The condition seemed somewhat better.

*Eleventh day.* The patient had several attacks of dyspnoea, especially after using the bed-pan. No heart murmurs were heard.

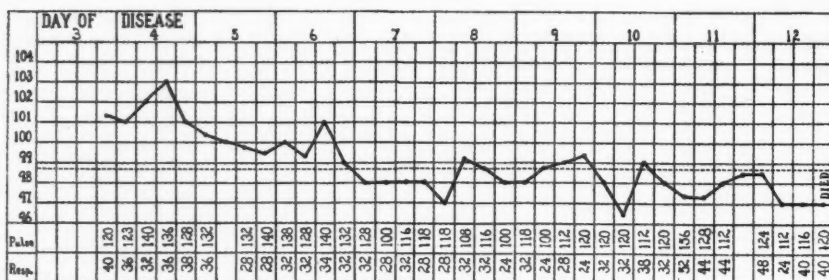
*Twelfth day.* There was some oedema of the feet and ankles. Sputum was profuse, nummular, and purulent. Smears showed very numerous fine Gram-negative bacilli, with the morphological characteristics of the influenza bacillus, and also a few diplococci (? pneumococci). Extreme sweating.

*Thirteenth day.* The condition was worse, the temperature subnormal. Death occurred at 2.0 a.m. after progressive circulatory failure.

*Temperature, &c.* The temperature during the third to sixth days was between 103° and 99°; after this it was never above 99.4°, and for the greater part of the time was subnormal. The pulse and respirations were much increased, even when the temperature was subnormal. The pulse varied from 100 to 156, and the respirations from 24 to 52 per minute. (See Chart I.)

*Diagnosis.* On the sixth day of illness the case was diagnosed as lobar pneumonia, and reported as such, but some doubt was entertained owing to the gradual onset and the uncertainty as to the exact date of commencement of the illness. Also, sibilant and sonorous râles had been heard over the consolidated lung, and this has not been a very common finding in our cases of lobar pneumonia. On the twelfth day the nummular character of the sputum, with the presence of

*B. influenzae* as the predominant organism in it, led us to change the diagnosis to influenzal broncho-pneumonia.





sputum and the presence of *B. influenzae* as the predominant organism in it; heart enlarged, no murmurs; dyspnoea and cyanosis increased; sweats, 'septic' temperature; death on sixth day. Post-mortem examination; bilateral capillary bronchitis and broncho-pneumonia; dilatation of right heart, hypertrophy of both sides; old endocarditis of aortic cusps (slight); acute vegetative endocarditis of aortic cusps and on otherwise healthy mitral cusps; large 'septic' spleen; slight chronic interstitial nephritis: cultures from the terminal bronchi and from the centre of the aortic vegetations yielded *B. influenzae* in pure culture; culture from heart's blood negative.

#### *Full Case Report.*

W. O., aged 44, admitted from local camp October 14, 1917, with diagnosis of broncho-pneumonia.

*Previous history.* Manual labourer in civil life. No illness of importance, but was much troubled with 'colds' in the winter. Two and a half years in army.

*Present illness.* Three days before admission, he took a swim in a near-by stream after getting overheated, and on the evening of that day his illness began with cough, hoarseness, pain in the chest, and diarrhoea. There was no definite chill, but he felt shivery and feverish. He reported sick the next day.

*Condition on admission (fourth day).* He was a large, heavily built man of florid complexion who looked the stated age. The face showed dilated venules, and the mucous membrane of the lips was cyanotic. The alae nasi were dilated and dyspnoea was marked. Labial herpes was absent. He was only comfortable when lying on the right side, and there was pain behind the sternum and on the left side when he was in any other position. Even when placed most comfortably some pain was felt on the right side on breathing. He was examined whilst in this position. There was poor expansion of the chest, and a slight diminution of resonance on percussion over almost the entire pulmonary area on both sides, but no actual dullness. Everywhere sharp metallic crepitations were heard, and these seemed very close to the bell of the stethoscope. In some places there were rhonchi and sibilant râles. No blowing breathing and no pleural friction were distinguished. When he was lying on the right side the heart appeared to be enlarged, the dullness extending one inch to the right of the sternum and the apex beat being in the left nipple line. The heart rate was increased, but neither at apex nor base were adventitious sounds heard. The pulmonary second sound was soft. The systolic blood pressure was 165 mm. of mercury and the diastolic 90 mm. (auscultatory method). There was no oedema of the feet or ankles. The sputum on the day of admission amounted to about 150 c.c., and was frothy on top, with some clear mucus, but the greater part was made up of heavier confluent masses of yellowish-white muco-purulent material. On the first examination a diagnosis of capillary bronchitis was made, and from past experience an influenzal infection was considered.

*Course of the disease (fifth day).* He was still very dyspnoeic and nothing new was made out from examination of heart and lung. There were about 90 c.c. of nummular sputum, such as we had learned to associate with capillary bronchitis due to *B. influenzae*. The individual masses were of moderate size, yellowish green in colour, muco-purulent, and quite discrete. Smears from this material showed very numerous bacilli with morphology and staining characteristics of the influenza bacillus.

*Sixth day.* The patient seemed to be somewhat easier in the morning. He had perspired very freely during the night so that his shirt had had to be changed several times. Sweating continued during the day. In the evening he became delirious and very dyspnoeic and died at 9.30 p.m.



*Temperature, &c.* The temperature was of the 'septic' type and showed 'spikes' to 103°, but was subnormal for twelve hours before death. The pulse ranged from 110 to 140 and the respirations from 32 to 52. (See Chart II.)

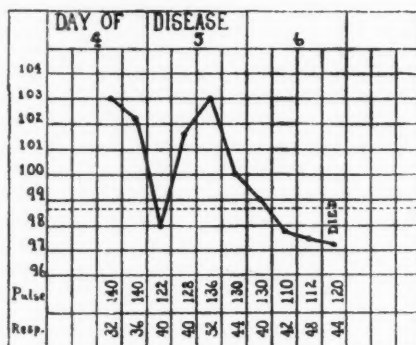


CHART II.

*Diagnosis.* Influenzal capillary bronchitis.

*Post-mortem examination.* Autopsy was performed about sixteen hours after death. *Thorax.*—The right pleural cavity showed a slight excess of clear fluid and a few old adhesions, and over the lower lobe was a patch of recent fibrinous exudate. Punctate subpleural haemorrhages were seen. The lungs were voluminous and oedematous, and the lower lobes congested. Throughout all the lobes could be felt small solid nodules, which on section were seen to be areas of broncho-pneumonia. In the right lower lobe these were more extensive and a confluent mass was found. From the smaller bronchioles in these areas greyish white pus exuded on pressure. The larger bronchi were acutely inflamed and contained muco-purulent exudate. *Heart.*—The heart was very large, the right side showing hypertrophy and dilatation, and the left side concentric hypertrophy. The pericardial cavity showed an excess of clear fluid. There were punctate subepicardial haemorrhages and an abundance of epicardial fat. The heart muscle was pale and showed fatty changes. The aorta was natural and free from old disease, but the free edge of the aortic cusps showed some sclerosis and thickening, and there were scarified areas at the sites of the corpora Arantii. The free edges of the cusps showed recent, granular, yellowish-red vegetations, the largest measuring 5 mm. in diameter. On the aortic cusp of the mitral valve, also, there was seen a small, rather flat, reddish, recent vegetation. This cusp showed no evidence of old disease. *Abdomen.*—The peritoneal cavity contained a small amount of clear fluid. The liver was large and smooth, the cut surface revealing an excess of fat. The spleen was very large, measuring 18×12 cm., and on section was very soft and diffuent. The kidney capsules stripped with some difficulty, and there was an increase of the fat in the pelves.

*Bacteriological examination.* Smears made from the pus which was squeezed from the bronchioles showed only bacilli with the characteristics of *B. influenzae*.

Cultures from the heart's blood were negative.

Smears from the centre of the vegetations on the aortic cusps showed no organisms, but cultures from this material yielded the influenza bacillus in pure growth.

*Characteristics of the organisms found in the cases reported.* The organisms seen in the smears from these cases and isolated in culture were delicate bacilli, non-motile and Gram-negative. They stained poorly with most of the ordinary stains, but readily with dilute carbol-fuchsin when heat was applied. With this latter dye polar staining was often so marked that the bacilli resembled minute diplococci. In culture they grew slowly, and only in the presence of haemoglobin. On the surface of human blood-agar the growth appeared as discrete, minute, dewdrop-like colonies, with no change in the colour of the medium, and these showed extreme transparency to transmitted light.

From the literature we have collected forty-five cases of endocarditis occurring in connexion with influenzal infection, in which there was more or less evidence pointing to the influenza bacillus as the cause of the lesion. In only fourteen of these cases are the data given sufficiently conclusive to justify an absolute diagnosis of influenzal endocarditis, according to the criteria which we have laid down at the commencement of this paper.

In addition to the above, we have reported two cases of acute endocarditis occurring as a complication of influenzal broncho-pneumonia, both coming to autopsy, and both yielding *B. influenzae* in pure culture from the vegetations on the heart valves. In neither case were blood-cultures made before death, nor was the presence of endocarditis suspected. Death occurred on the thirteenth and sixth days of illness respectively. In both cases the lesions of the lung were found at autopsy to be very extensive, and we consider that these were the direct cause of death.

It is of interest to note that in the first of our cases the recent vegetations on the aortic cusps were found on a valve already injured (probably by syphilitic infection), and that in our second case the fresh lesions of the aortic valve were also engrafted upon the site of an old inflammatory process, although in this case there was also a vegetation on the mitral valve which revealed no evidence of previous disease. It is not clear from Lebreton's collected series in what proportion of cases the acute endocarditis arose on an already damaged valve, but he expressly states that healthy valves, as well as injured ones, may be attacked in the course of an influenzal infection. Simons remarks on this point; and we cannot understand (when he states that influenzal infection is never found save in chronic cases) whether he means that the organism produces a chronic condition, or that the infection is always implanted on a previous chronic lesion.

Simons, and also Libman and Celler, have drawn attention to the occurrence of painful erythematous nodules associated with influenzal endocarditis. These were not present in our cases.

We should like to call attention to the care necessary for the isolation of the organism at autopsy. In our second case, culture from the heart's blood was negative. In the first case it was positive, but smears and cultures from the surface of the granulations gave a negative result, although the material from the centre of the lesions yielded a pure culture and showed numerous bacilli in

the direct smear. Also, in both of Horder's cases, culture from the heart's blood was sterile, although blood culture during life had repeatedly yielded *B. influenzae*, whilst smears and cultures from the vegetations at autopsy showed the organism in large numbers. Similarly, Marmorstein failed to recover the organism from the vegetations in one of his cases, although in the same case he obtained it from the embolic lesions in the brain.

During the recent epidemic, which, at the time of writing (August 1918), has come to a standstill, autopsies were performed on eleven fatal cases of broncho-pneumonia. From seven of these *B. influenzae* was obtained, but no lesions of the endocardium were found.

## BIBLIOGRAPHY.

1. Austin, Mabel, 'Influenzal Endocarditis', *Johns Hopk. Hosp. Bull.*, Baltimore, 1899, x. 194.
2. Horder, T. J., 'Bacillus Influenzae as a Cause of Endocarditis', *Trans. Patholog. Soc.*, Lond., 1906, lvii. 58.
3. Isambert, 'Hémococcobacillémie', *Thèse de Nancy*, 1901.
4. Jehle, *Wien. Klin. Wochenschr.*, 1899, xii. 129.
5. Lebreton, 'L'Endocardite grippale', *Thèse*, Paris, No. 196, 1912.
6. Libman and Celler, 'Observations on the Etiology of Subacute Infective Endocarditis', *Trans. Assoc. Amer. Physicians*, 1910, xxv. 5-19.
7. McPhedran, J. H., 'Some Remarks on Endocarditis in Influenza', *Canad. Med. Assoc. Journ.*, Toronto, 1913, N.S. iii. 572-4.
8. Marmorstein, M., 'Contribution à l'étude des Aortites grippales', *Revue de Méd.*, Paris, 1908, xxviii. 267.
9. Mathers, George, *Jour. of Infectious Dis.*, Chicago, 1917, xxi. 1.
10. Moinet, *Thèse de Lyon*, 1892.
11. Presslich, 'Einiges über Endokarditis bei Influenza', *Wien. Med. Presse*, 1905, xlv. 69 and 131.
12. Schlagenhauser, 'Ein Fall von Influenza Endocarditis der Aortenklappen u. des offenen Ductus Botalli', *Zeit. f. Heilkunde*, 1901, xxii. 19.
13. Simons, Irving, 'Critical Review, Bacterial Endocarditis', *Quart. Jour. Med.*, Oxford, 1913-14, vii. 291.
14. Smith, F. J., 'The Influenza Bacillus as a Cause of Fatal Endocarditis after Eight Years (?)', *Lancet*, Lond., 1908, i. 1201.

## THE THERAPEUTIC ACTION OF DIGITALIS ON THE RAPID, REGULAR, RHEUMATIC HEART

By G. A. SUTHERLAND

### *Introduction.*

THERE is a considerable difference of opinion still in existence as to the exact action of digitalis on the heart, and as to the exact type of case in which it is suitable. As regards auricular fibrillation all are agreed that digitalis acts beneficially, and this is no new discovery, for it was in the type of case now known as auricular fibrillation that digitalis established its reputation many years ago.

From a correspondence in the *Lancet*, 1917, I take the following extracts. Sir John Broadbent said: 'Any clinician knows the extraordinarily satisfactory results obtained from the administration of digitalis in cases of heart failure and dropsy associated with mitral incompetence, *even when the pulse is quite regular and there is no question of auricular fibrillation*' (1). To this statement Dr. Thomas Lewis replied as follows: 'In regard to digitalis there is on record at the present time a large number of cases of auricular fibrillation in which the effects of the drug have been observed closely, and in which the rate of the ventricle has been shown beyond doubt to be controlled by the drug. There is no comparable series *in which, with a normal sequence of chamber contraction, digitalis has been shown to have a similar effect or, in fact, any striking beneficial effect.* If Sir John Broadbent can compile such a series; if he can place on record a number of observations in which "extraordinarily satisfactory results" follow the administration of digitalis when the heart's action is regular; if he can show that these results come from the administration, and not from other factors in the patient's environment (as has been done in the case of those suffering from fibrillation), I for one will freely acknowledge that he has performed for mankind generally and for his fellow practitioners a signal service. But the bald statement that it is so is valueless; the series is not now forthcoming, and until it is forthcoming the conclusion cannot gain acceptance' (2).

The point at issue between these disputants is as to whether digitalis ever acts beneficially on a regular heart—that is, a heart in which the normal rhythm is present. The question of rapidity of action is not referred to. The purpose

of this paper is to show that a regular heart showing signs of failure may be beneficially acted on by digitalis. Such an effect, in my experience, is produced only when the heart is acting rapidly, and the mode of action consists solely in slowing the cardiac rate, thus leaving the ventricles free to contract more powerfully.

## I.

*On normal rhythm with rapid rate.* In the case of damaged hearts—that is to say, hearts which have become impaired in their function by endocardial, myocardial, or pericardial disease—the successful carrying on of the circulation depends on the automatic or inherent power in the heart to make good for the damage done, the so-called compensatory power of the heart. These compensatory changes in the heart cannot be regulated by direct therapeutic measures, and can be influenced only indirectly by securing rest and freedom from disturbance to the heart while the recuperative action is taking place.

Disturbance of a damaged heart which has been more or less fully compensated usually takes one of two forms, either an acceleration of the rate or a disorder of the rhythm, while not infrequently both of these are present. Auricular fibrillation is the most familiar example of disturbance of the rate and rhythm of the heart. This form of disturbance may affect adversely the working of the most complete compensatory changes and lead to serious cardiac failure. When this condition is carefully examined it will be found that the action of the disturbing factor (fibrillation) is to increase the ventricular rate, and from this follows inability of the ventricle to maintain efficient contractions when working at that rate.

Experience has taught us that a persistent acceleration of the cardiac (ventricular) rate has an injurious effect on the cardiac efficiency. It has such an effect in time on a heart which was previously healthy, for example in Graves's disease, and it has this effect much sooner on a heart which is already damaged. As a rule a marked acceleration of rate is also associated with some disturbance of the rhythm of the heart, and it is this association which has attracted attention and has led to much investigation recently. But there are also to be met with hearts already impaired by gross disease, which show a persistently rapid and regular action, with a normal rhythm. The subjects of this condition may in time manifest signs and symptoms which are those of cardiac fatigue, cardiac weakness, and cardiac failure—that is to say, symptoms which are indicative of progressive cardiac inefficiency. It can be demonstrated that these indications of cardiac inefficiency are dependent on the accelerated rate and not on the gross underlying disease. The demonstration is made by means of digitalis treatment, for if the heart rate is slowed by full doses of that drug the symptoms and signs disappear without any evidence that any change has taken place in the heart save the slowing of the rate.

The opinions expressed above as to the action of digitalis are not at present generally accepted, nor are they acted on in practice. One of the most important papers on the subject of digitalis is that by Sir James Mackenzie (3). He showed conclusively the beneficial action of digitalis in cases of auricular fibrillation—that is to say, in the chief form of abnormal rhythm associated with cardiac failure. As regards the action of digitalis on hearts with a normal rhythm he drew the following conclusions :

‘As a result of these observations, so far as slowing of the heart’s rate is concerned, it may be laid down as a law, that the reaction to digitalis is far less effective when the rhythm is normal than when there is auricular fibrillation’ (p. 279).

‘While there is no doubt that digitalis relieves distress of breathing and reduces dropsy, it does not do so necessarily by slowing the pulse. The rate of the heart in cases of aortic regurgitation, with the normal rhythm, is not affected, or very slightly, in my experience. In patients with the normal rhythm digitalis has induced irregularities of the heart’s action of the following forms: (1) sinus irregularities, (2) extra-systoles, (3) partial heart-block, (4) *pulsus alternans*’ (p. 290).

‘In cases with the normal rhythm the improvement was not very marked as a rule, and in most of them it is doubtful whether the rest alone was not sufficient to account for the slight improvement’ (p. 280).

As regards the cases of heart disease with a normal rhythm which he describes and analyses, one notes that these were cases showing an advanced stage of cardiac degeneration. The patients were suffering from the effects of degenerative changes consequent on long-standing disease. This is not the stage of disease in which we can hope to secure our greatest therapeutic results. If Sir James Mackenzie had devoted some attention to the early stages of cardiac disease and the effects of treatment at that stage he might have been led to modify his views as to the uselessness of digitalis in cardiac cases with a normal rhythm. One notes, also, that in his cases of normal rhythm the cardiac rate was usually normal or only slightly raised, and that no benefit followed the use of digitalis. He gave a most illuminating chart (p. 286) showing the effect on the heart rate in a series of cases of auricular fibrillation, and in another series of cases of normal rhythm, both of which were treated with full doses of digitalis. In the former the average heart rate at the beginning of treatment was 112, and at the end it had fallen to 64; in the latter the initial heart rate was 78, and at the end of treatment it was 75. In the former class the average heart rate per minute was lowered by 48 beats, and in the latter by 3 beats. He would seem to have established the facts that a heart beating with a normal rhythm at a normal rate, (1) is not affected, to any appreciable extent, as regards the rate by medicinal doses of digitalis, and (2) is not beneficially acted on by digitalis. These conclusions I am prepared to accept, not only because they have the support of Sir James Mackenzie’s authority, but also because they are confirmed by my own experience. The conclusions, however,



do not bear directly on cases occurring in early life, where the rhythm is normal but where the cardiac rate is much accelerated.

It is the object of this paper to show that there is a class of case with a persistently rapid and regular heart rate, due to rheumatic infection, in which the acceleration can be controlled by digitalis in medicinal doses. Further, this action is as specific as in the case of the treatment of auricular fibrillation, and the beneficial effects are as striking.

## II.

*The type of case selected.* Amongst those who have passed through an attack of acute or subacute rheumatic infection there are many who show a persistently accelerated cardiac rate. We do not refer to a slight acceleration of rate, such as would be represented by 100 beats per minute, but a rising of the rate up to from 115 to 130 beats per minute. The objective signs of disease in the heart vary; in some there are evidences of valvulitis only, in others of myocardial changes, for example dilatation, and in others of adherent pericardium. At present we cannot correlate the evidences of gross cardiac disease with acceleration of rate except so far as to assume that if the cardiac acceleration is not nervous in origin there is probably some myocardial change, organic or toxic, disturbing the normal pacemaker. Whatever the gross lesions of the heart were in the cases selected there were sufficient compensatory changes to allow of the circulation being carried on, although with diminished efficiency. So far as the treatment by digitalis was concerned, the gross lesions were not considered as of primary importance, and clinically no effect on them was ever detected save such as followed from slowing of the heart rate.

If active signs of rheumatic infection were present, as indicated by a temperature above 99°-100°, digitalis was not given until the temperature had been reduced by means of salicylate of soda or had fallen to normal. Pyrexia, whether rheumatic or non-rheumatic, seems to check or abolish the action of digitalis. If the temperature was apyrexial, the presence of rheumatic subcutaneous nodules, of passing eruptions of erythema, or of fleeting articular and muscular pains did not appear to affect the treatment prejudicially.

The patients were all under the age of fourteen years. As a matter of experience it is found that an accelerated cardiac rate following rheumatic infection is extremely common during childhood, and also that it is very persistent. It is often the one persistent condition which leads the physician to enjoin prolonged rest in bed. This type of case, therefore, seemed specially suitable for testing the slowing action of digitalis and observing any effects which followed.

In all the cases rheumatic infection had undoubtedly been present, and so far as could be determined there was no mixed infection at the time. Further, it seemed clear on clinical evidence that the acceleration of rate was primarily

cardiac in origin and was not due to nervous disturbance or latent toxæmia (non-rheumatic). A nervous source of disturbance was ruled out by the fact that the rate of the heart was as rapid during sleep as during the waking hours.

### III.

*The reasons for treatment.* In this class of case the question may arise, Why is treatment by digitalis called for? It may be urged that under rest in bed an accelerated heart rate—if the physician views it as a bad sign—will in time settle down. The advantage of rest in bed in this condition is undeniable, and prolonged rest has been extensively employed by all of us in the past, whenever circumstances rendered it possible. But it has also its disadvantages. An indefinite prolongation of rest in bed is by no means suited to the healthy growth and development of a child, nor does it tend to increase the resisting powers of the patient against fresh outbreaks of rheumatic infection. On the contrary, it seems rather to predispose to them, as is shown by the frequent recurrences during prolonged rest. In our efforts to restore the heart to healthy action we must not neglect or injure the patient's general condition. Further, most of the cases on which this paper is based had had rest, and even prolonged rest, without obtaining benefit as regards the acceleration of the heart rate. There was apparently some disturbing factor present in the heart itself, which maintained this rate, and which called for more active treatment and more prompt relief.

In addition to the acceleration of rate, and in our view as the result of it, there were signs and symptoms in the patients which seemed to call for treatment, although the extent to which the cardiac functions were affected varied considerably.

In one class we had patients who presented no symptoms while in bed and who could walk about. But they were easily rendered breathless on any exertion, and they manifested no desire to take active exercise. In other words, fatigue of the heart was easily induced, and the accompanying symptoms rendered the patient disinclined for exertion. This condition called for relief if possible.

In another class the rest power of the heart as well as the reserve power was giving out. Even while at rest symptoms such as breathlessness were present. Signs of failure of the circulation were to be found in a large and engorged liver, in general oedema, or in pulmonary oedema, and in oliguria. The patients in this class were incapable of making any exertion without great discomfort, and were progressing towards complete cardiac failure. Treatment was clearly called for in order to obtain and maintain an efficient circulation.

## IV.

*Mode of action of digitalis in slowing the heart rate.* The striking results from digitalis therapy are best seen in cases of auricular fibrillation, and those who have followed Mackenzie's teaching on the subject have convinced themselves of the truth of his statements. There is not the same unanimity of opinion on the question as to whether in fibrillation digitalis acts directly on the cardiac muscle or through the vagus nerve. All are agreed, however, that the slowing of the ventricular rate is brought about by the induction of partial heart-block, and that this is effected by some change in the auriculo-ventricular node and bundle following the administration of digitalis. So far as my own experience goes in cases of cardiac failure with a normal rhythm and a normal rate the action of digitalis is the same—that is to say, it induces partial heart-block without affecting in any way the auricular rate (and without any benefit to the patient).

Under all normal and many pathological conditions the sino-auricular node (or 'pacemaker of the heart', as Lewis terms it) determines the rate of the heart. In auricular fibrillation digitalis does not affect this node because it is thrown out of action as long as the auricles are fibrillating. Its function as pacemaker has been temporarily or permanently abolished owing to the abnormal discharge of stimuli from innumerable foci in the auricles. In fibrillation, therefore, we cannot expect digitalis to have any effect in slowing the heart through the sino-auricular node. Again, in many, one may say most, of the cases of acceleration of the heart rate (for example, fevers, toxæmia, &c.) where the sino-auricular node determines the heart rate and is clearly being stimulated to over-action, we know that digitalis has no appreciable effect on the heart rate.

In the class of case we are dealing with there is one constant factor, namely, rheumatic infection, and experience has shown that it is on the rheumatic heart that digitalis has its most potent action. The conclusion we came to was that the acceleration of the cardiac rate was due to the activity of the sino-auricular node having been directly affected by the rheumatic infection. When the auricular and ventricular rates are similarly increased, and the arterial and venous tracings show a regular and normal rhythm, as they did in these cases, we may reasonably assume that the acceleration of rate is due to some disturbance of the normal action of the sino-auricular node. The only direct method of slowing the heart rate as a whole seemed, therefore, to be by an inhibitory action on the sino-auricular node. We had had no previous experience in this connexion of the results of digitalis treatment, because our successes with that drug had always been in cases presenting an abnormal rhythm which had thrown the sino-auricular node out of action. One case successfully treated on the above lines seemed to justify a further trial of digitalis.

It was expected that digitalis would produce its effect, if any, through the inhibitory action of the vagus nerve, but the question as to whether the action

was through the vagus or directly on the sino-auricular node need not detain us here. The assumption that digitalis acts on the heart through stimulation of the inhibitory action of the vagus serves very well as a basis for clinical work. It was recognized that in order to check the over-action of the sino-auricular node full doses of digitalis would probably be required, as former tests with small doses continued over a long period had failed to give any results.

## V.

*Clinical methods and results.* A number of cases which seemed suitable were treated and the results as regards slowing of the heart were uniform. Ten of these are given in detail at the end and the results obtained from them are here summarized. These patients were all under observation in hospital, so that the records could be made with regularity and precision. The results obtained in the case of other patients who were seen only at intervals supplied corroborative evidence of the results obtained in the wards.

The ages of these patients ranged from five to thirteen years. The gross valvular lesions were mitral incompetence, mitral stenosis, and aortic incompetence, but from the point of view of treatment the one thing we were concerned with was the rapid cardiac action.

In order to secure a standardized preparation of digitalis we used Nativelle's digitalin granules, containing gr. 1/240 or gr. 1/600 in each, or Burroughs, Wellcome and Co.'s tabloids of crystallized digitalin, gr. 1/250. As was to be expected, the larger the dose the speedier was the result. It is to be noted in these cases, as has been noted in the use of digitalis in auricular fibrillation, that it is the total amount taken which is the decisive factor (Table, p. 190). In the case of these young patients it may be stated that the full slowing effect was produced when from gr. 1/10 to gr. 1/50 of crystallized digitalin had been taken. After the required amount had been taken to produce full slowing of the pulse we usually found that during the period of twenty-four hours when this has occurred the patient also complained of nausea or actual vomiting, of loss of appetite, and of distinct malaise. Experience has shown that the administration of digitalin, gr. 1/240 every six or eight hours, will act efficiently in young patients, and will not act injuriously if the drug is stopped when the pulse is fully slowed or when vomiting comes on. The corresponding dose, if the tincture of digitalis were used, would be from forty-five to sixty drops daily. When the desired effect has been obtained the digitalin treatment should be stopped for a few days, and then resumed if necessary, but always in much smaller doses than during the original course. Speaking generally, we may say that one-quarter of the original daily dose will suffice to maintain the slowing effect. The variations in different cases will be seen in the appended list.

Full slowing after	No. of Doses.	Amount per Dose.	Total Amount Digitalin.
3 days	15	gr. 1/600	= gr. 1/40
7 days	21	gr. 1/240	= gr. 1/11
3 days	9	gr. 1/240	= gr. 1/26
3 days	7	gr. 1/240	= gr. 1/34
3 days	5	gr. 1/240	= gr. 1/48
9 days	40	gr. 1/600	= gr. 1/15
3 days	9	gr. 1/240	= gr. 1/27
5 days	8	gr. 1/240	= gr. 1/30
6 days	14	gr. 1/240	= gr. 1/17

Average amount digitalin required = gr. 1/27.

Table showing dosage and duration of digitalin treatment to procure full slowing in nine cases of rapid heart.

In all the cases of the type we have designated, except those who were suffering from a very advanced stage of cardiac disease, definite slowing of the heart rate followed the administration of digitalis. This slowing was accompanied by great improvement in the efficiency of the cardiac action, and in the patients' general condition.

Six cases (Nos. 1, 2, 4, 5, 6, 7) have been grouped together and analysed as to the effect of digitalis on the heart rate (Fig. 1). The average cardiac rate of the group before treatment was 124 beats per minute, and on the fifth day after treatment was begun it had fallen to 82 beats. This represents a lowering of the average heart rate by 42 beats per minute. In the case of these young subjects a reduction of the rate to 82 beats per minute may be regarded as a full slowing action. In some cases the rate fell as low as 48 beats per minute, without any bad effect on the patient or the cardiac action. The full benefit of the drug seemed to be assured when the rate had fallen to, and was maintained at, from 80 to 85 beats per minute. The lower rates are apt to be accompanied by a marked degree of sinus irregularity, which rather points to over-stimulation of the vagus nerve.

It may be suggested that the slowing of the heart rate was due to rest in bed and hospital surroundings generally. In the accompanying series of cases it will be seen that the effects of digitalis pass off when the drug is stopped. Opportunities thus presented themselves of repeating the test, and it was invariably found that the same slowing effect of digitalis could be reproduced as required. This was found to be possible both in the case of ward patients and of those who had become out-patients. The test has been made so frequently that it may confidently be stated that the slowing effect was due to digitalis and to no other cause.

The time necessary for securing full slowing of the pulse, that is a rate between 80 and 85 per minute in young subjects, varies in different cases and with the dosage. We found that on full doses it usually followed after three or four days, but with smaller doses it might be any time up to nine

days. As regards an early and definite slowing of the heart as indicated by a diminution of 20 beats per minute in the pulse-rate we found amongst six patients that this occurred after one day's treatment in one case, after two days' treatment in four cases, and after three days' treatment in one case. This would appear to be an earlier action of digitalis than is usually noted in the case of auricular fibrillation.

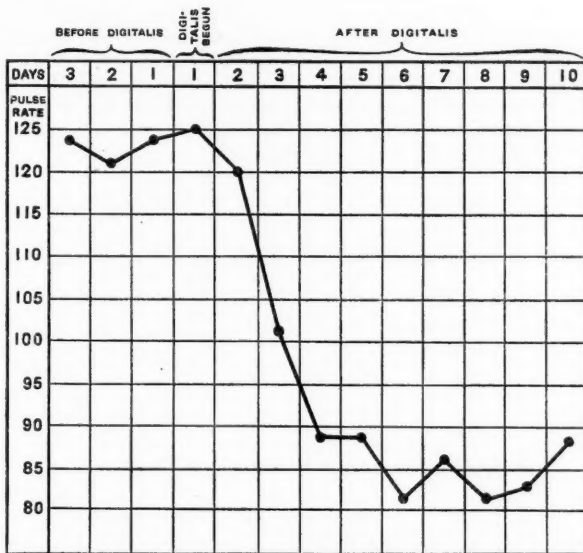


FIG. 1. Chart showing the effect of digitalis on the pulse-rate in six cases of rapid, regular cardiac action, with normal rhythm. The mean of the daily rate in the six cases is charted.

Polygraph tracings taken before treatment and after slowing had taken place showed that the normal rhythm of the heart had persisted throughout, and that the action of the digitalin had been on the sino-auricular node. In some of the cases marked irregularity of the heart rate accompanied the slowing, but it was a sinus irregularity, a prolongation of the diastolic pause at times without any disturbance of the normal cardiac rhythm (see Figs. 2, 3, 4). In some of the cases the sinus irregularity was clearly associated with respiration, and was, therefore, to be regarded as merely the 'youthful type of irregularity' (Mackenzie). In others, however, there was a distinct 'phasic variation' (Lewis), which is known to result from the action of digitalis. In this form of irregularity, which is also of sinus origin, the heart rate changes during periods of variable duration, all being slow, but some slower than others. In some cases the sinus irregularity took the form of varying diastolic periods, so that in a tracing no two consecutive beats were followed by the same length of diastolic pause. Another variety of irregularity in the form of extra-systoles was present in some cases, accompanying the slowing, and usually passing off



entirely within forty-eight hours of the cessation of digitalis. This also is a recognized effect of digitalis on the cardiac action (Mackenzie, Lewis). The other forms of irregularity under digitalis to which Mackenzie has drawn attention, namely, partial heart-block and the pulsus alternans, were not found, but would probably have appeared had the large doses of digitalis been continued after the slowing effect had been produced. The practice was to stop the digitalis when the heart had been definitely slowed, or when vomiting occurred.

It would appear, therefore, that the inhibitory action of the vagus told on the disturbed cardiac area, the sino-auricular node. In auricular fibrillation treatment by means of digitalis is directed to the securing of a special action,

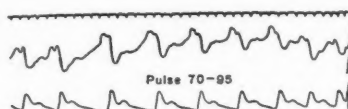


FIG. 2. Sinus irregularity.

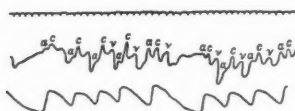


FIG. 3. Respiratory irregularity.

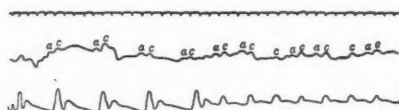


FIG. 4. Phasic variation.

namely inhibition, on the over-action of a certain area of the heart, namely the auriculo-ventricular node and bundle, and we expect a slowing of the ventricular rate and relief of symptoms to follow. In the class of case we are dealing with, treatment by means of digitalis was directed to a special action, namely inhibition, on the over-action of a certain area of the heart, namely the sino-auricular node, and we hoped to obtain a slowing of the auricular and ventricular rates with benefit to the patient's condition as the result. These precise methods have many advantages over the former ones, which consisted in discharging at the heart as a whole 'cardiac tonics', the exact action of which was unknown, and the effects of which were, to say the least, extremely problematical.

The effects of the slowing of the heart were distinctly beneficial. In some cases pre-existing dilatation of the heart was definitely diminished, while in others no appreciable change in the size of the heart occurred. Murmurs which had temporarily disappeared, owing to the feebler contractions of the heart

when beating quickly, became audible again when the heart rate was slowed and the contractions became stronger. More especially was this the case as regards the presystolic murmur in mitral obstruction and the diastolic murmur in aortic regurgitation. When enlargement of the liver was present as the result of venous congestion, it invariably passed off soon after slowing of the heart took place. Perhaps the best test of the relief afforded was in connexion with the breathing. Objectively, it was found that the number of respirations per minute fell when the breathing had been hurried, and that the signs of dyspnoea, when present, rapidly subsided. Pulmonary oedema cleared off. Subjectively, the patient experienced great relief as regards the dyspnoea. The power of taking exercise without dyspnoea was markedly improved in all cases. In a case with generalized oedema, oliguria, &c., complete relief followed the slowing of the heart rate. Even more striking than the objective changes was the improvement in the patients' general condition as manifested by their spirits, their enjoyment of life, and their desire for more active exercise than they had previously been able to take.

Auricular fibrillation tends after a time to become a permanent condition, probably owing to the organic changes in the heart which induce it. In the type of case we are now dealing with the rapid action of the heart is presumably due to present or past toxæmia (of rheumatic origin), and such organic changes as may have taken place in the heart are not responsible for the quickened rate. There is no evidence that the sino-auricular node is organically or permanently affected.

We have been able in these cases to improve the cardiac efficiency by slowing the rate. We have also been able to maintain this result by continuing the use of digitalis in smaller doses. The further question arose as to how long the treatment by digitalis must be continued. It was found that this varied in different cases.

It would appear that the elimination of the rheumatic infection from the blood and from the cardiac tissues is an essential condition before the heart can be expected to resume and maintain its normal rate. In some cases this is a matter of weeks, and in others of months, as is shown in the appended cases. These cases also show that, unlike the disturbance known as auricular fibrillation, the disturbance at the sino-auricular node leading to the rapid cardiac rate is by no means to be regarded as permanent. It is a functional disturbance and not an organic change. It is an additional disability in a heart already impaired by organic changes, valvular or myocardial. It is usually a transitory effect of rheumatic infection, provided that the infection passes off. It tends to persist as long as the rheumatic infection is active.

Unfortunately, during the period of life we are dealing with, the rheumatic poison smoulders long in the system, bursting out at times into varying degrees of activity. As long as this condition persists the liability to disturbance of the sino-auricular node and a rapid heart rate will always be present. It may be necessary to alternate periods of salicylate treatment with periods of digitalis

treatment. This state of affairs may continue for some years until the patient has outgrown the tendency to fresh rheumatic attacks.

In other cases the rapid heart rate persists after an attack of acute or subacute rheumatism, and when the pyrexia has ceased. The quickened rate may continue for a varying length of time, during which the patient is usually kept in bed, both as a precautionary measure and because the heart's action is undoubtedly weakened by the rapidity of the rate. Digitalis can be employed at this time to slow the rate and thus prevent any further weakening of the heart's action. By this means the period of convalescence is much shortened, and the prolonged rest in bed, which cautious physicians have as a rule enforced, is rendered unnecessary.

At the same time the limitations of digitalis as a remedial agent in these conditions must be clearly understood. We are not using digitalis as a general cardiac tonic but as a check on the rapid cardiac rate. We assume that the heart is suffering as regards its efficiency because of the rapid rate. We do not expect to make the heart sound by means of digitalis, but to restore it to the condition it was in before the rapid rate was initiated. For example, in a case of mitral stenosis following rheumatic infection, there may have been some associated dilatation of the right heart and shortness of breath on exertion, although the rate was normal. This condition may have lasted for months or years, and then there develops a great increase in the heart rate and, in association, increased dyspnoea, enlarged liver, oedema, &c. All that we claim for digitalis is that it restores the *status quo ante*, the pre-tachycardia rate, and at the same time the symptoms due to the rapid rate are relieved. It is believed by many that in some wonderful way digitalis tones up the heart and strengthens its muscular tissues. Of that we have no experience and to that we make no claim. We have never been able to change in any way permanent cardiac lesions or permanent cardiac symptoms due to these lesions. A similar experience holds good in the case of auricular fibrillation. No one has been able by means of digitalis to cure auricular fibrillation or the underlying cardiac changes which give rise to fibrillation. So that in no sense is digitalis to be regarded as curative of cardiac disease, but it affects, and affects beneficially, the disturbance in rate which is the result of cardiac disease. If the limitations of digitalis as used in cases of the rapid, regular, rheumatic heart are recognized one will not only appreciate the good it can do, but one will also be saved from expecting too much and from being disappointed in that it cannot make a diseased heart sound again.

I have proved to my own satisfaction, and am now trying to prove to the satisfaction of others, that in the type of case described one can prescribe digitalis with as much confidence in its efficient and beneficial action as in cases of auricular fibrillation. In the former digitalis is given with a view to its acting on the sino-auricular node, while in the latter its action is directed to the auriculo-ventricular node and bundle. In both cases what we aim at and secure by means of digitalis is a slowing of the ventricular rate, and provided

that there is a sufficiency of sound contractile tissue in the ventricles, the natural powers of the heart are then capable of restoring a weakened or failing circulation.

## REFERENCES.

1. Broadbent, Sir J., *Lancet*, Lond., 1917, i. 965.
2. Lewis, T., *ibid.*, 1013.
3. Mackenzie, Sir J., 'Digitalis', *Heart*, Lond., 1910-11, ii. 273.

## CASES.

*Case I. E. S. E., female, 6 $\frac{3}{4}$  years. Chorea. Carditis. (?) Mitral Stenosis. Rheumatic nodules. Rapid heart, normal rhythm, digitalis slowing.*

Patient was admitted suffering from chorea on May 18, 1916; she had suffered on and off for three years from rheumatism, chorea, and heart disease. Short of breath on exertion. The left side of the heart was not enlarged, but there was increased pulsation of the right side, and (?) presystolic and systolic murmurs were heard at the apex. Many rheumatic nodules were present. There was slight irregular pyrexia at first, moderated by salicylate treatment.

The cardiac rate was persistently rapid, varying from 120 to 142 per minute, and the respirations were 24 to 28. The child had no active symptoms of distress while in bed, there was no oedema or oliguria, and the temperature being for the most part under 99° F. did not explain the rapid cardiac action.

A course of digitalis was given and the results are shown here.

Date.	Doses of Digitalin gr. 1/600.	Pulse-rate.	Remarks.
June 2	—	130	Tracings show normal sinus rhythm
3	—	122	
4	—	128	
5	—	120	
6	2	124	
7	6	116	Digitalin begun
8	5	116	
9	5	124	
10	5	126	
11	5	112	
12	5	100	
13	5	98	
14	2	82	
15	—	86	
16	—	80	
17	—	80	Vomited once. Digitalin stopped. Tracings show normal sinus rhythm
18	—	94	

There was a definite slowing of the heart rate after a few days, which amounted to 44 beats when full slowing was obtained. The maximum effect was reached on the three days following the stoppage of the drug; the effect continued to a less extent for twelve days, and then the previous rapid rate was reached and persisted. Tracings taken before and after the digitalis treatment showed that

the rapid heart action was of the normal sinus rhythm, and that the slower rate obtained was of the same nature. There was no evidence of heart-block. No change could be made out in the physical signs of the heart save the slower rate. As the patient was in bed throughout and free from symptoms while at rest, the effect of the drug on symptoms could not be estimated.

She became an out-patient and digitalis treatment was resumed.

18.10.16. P. = 120. Cardiac dullness extends  $\frac{3}{4}$ " to right of mid-sternum. No left-sided dilatation. Liver extends to within 2" of umbilicus. Epigastric pulsation marked. Ordered Tr. digitalis,  $\mathcal{O}$  xv t. d. s.

30.10.16. P. = 116. Has been getting about, but short of breath. Vomited this morning. Medicine stopped.

1.11.16. P. = 104. Ordered two tabloids digitalin (gr. 1/250) daily.

4.11.16. P. = 90. Vomiting after four tabloids.

8.11.16. P. = 84. No dyspnoea on exertion, no enlargement of the liver, or of the right side of heart. Ordered digitalin gr. 1/500 daily.

11.11.16. P. = 84.

22.11.16. P. = 86.

29.11.16. P. = 98.

20.12.16. P. = 116. She was suffering from bronchitis and a fresh attack of chorea. Sent into hospital.

2.7.17. Aged  $7\frac{1}{2}$  years. Patient has been at a convalescent home for five months. The breathing is good on quiet walking, but she gets short of breath on any exertion. There is considerable right-sided enlargement of the heart, none on the left side. A systolic murmur is audible at the apex, following a ringing first sound. A presystolic thrill is present, but no definite murmur.

P. = 84, regular. On exertion, P. = 110.

*Case II. E. L. L., female, 11 years. Acute rheumatism. Mitral and aortic regurgitation. Rheumatic nodules, and erythema. Cardiac dyspnoea. Rapid, regular cardiac action, normal rhythm, digitalis slowing.*

This patient was admitted to hospital suffering from rheumatic fever with pain and effusion in both knee-joints. There was a history of articular pains in the hands five years previously. The acute manifestations subsided rapidly under the use of salicylate of soda. On admission the cardiac action was rapid, there was dilatation of the left side, the apex beat being  $\frac{3}{4}$ " outside the nipple line, and a loud systolic murmur was audible at the apex. A fortnight later, when the heart rate had settled down, a double murmur was heard at the apex and the diastolic part was evidently conducted from the aortic valve as its maximum intensity was in the third left intercostal space. There was evidence of mitral and aortic incompetence. She remained six weeks in hospital, had occasional relapses of subacute rheumatism, and on discharge showed a cardiac condition as described above.

She was seen again three months later, complaining of shortness of breath on exertion and that any walking caused great fatigue. The pulse averaged about 100 per minute, the volume was small, and there was no collapse during diastole. The only change in the cardiac condition was an increased heave at the apical region due to hypertrophy.

Three months later she was readmitted from a convalescent home owing to increasing dyspnoea. For the previous three weeks the cardiac rate had averaged from 120 to 130 beats per minute, and she had been confined to bed for a fortnight owing to breathlessness. There was no pyrexia and no evidence of active infection. Praecordial pulsation was strong and heaving and the left side of the heart extended  $1\frac{1}{2}$ " outside the nipple line. Murmurs of mitral and aortic regurgitation were present. The cardiac rate averaged 124 beats per minute. The liver was enlarged, extending 2" below the costal margin. Polygraph

tracings showed a pulse-rate of 125, with perfectly regular and normal cardiac rhythm. A few rheumatic nodules were present on the elbows, but there was no other evidence of active rheumatic infection. After a fortnight's rest in bed and salicylate treatment there was no change in the cardiac rate or the breathlessness, and it was resolved to try digitalis treatment. The action of digitalis in slowing the heart is shown in the accompanying table. Four days after the digitalis

Date.	Doses of Digitalin gr. 1/240.	Pulse-rate.	Remarks.
Sept. 10	—	124	Dilatation and hypertrophy of left ventricle : dilatation without hypertrophy of right ventricle. Liver enlarged
11	—	132	
12	—	128	
13	—	104	
14	—	120	Tracings show a rapid, regular cardiac action with normal rhythm
15	—	124	
16	2	120	Digitalin begun
17	3	120	
18	2	96	Vomited twice
19	—	86	Edge of liver at costal margin
20	—	84	
21	1	72	Slow regular action of heart except for slight variation in length of diastole. Apex beat $\frac{1}{2}$ " outside nipple line. Tracings show a normal sinus rhythm
22	1	80	
23	1	64	
24	—	60	
25	1	76	
26	—	76	
27	1	68	Digitalin stopped
28	—	68	After running round the ward slight dyspnoea and a pulse-rate of 124, which soon returned to normal
29	—	68	

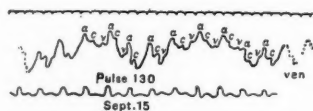


FIG. 5.

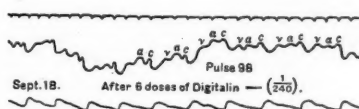


FIG. 6.

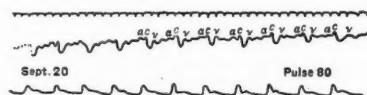


FIG. 7.

was begun the heart was beating regularly at 80 per minute. Tracings showed that the rhythm was a normal sinus one. (See Figs. 5, 6, 7.) The apex beat was only  $\frac{1}{2}$ " outside the nipple line, and the right border of the heart did not extend beyond the right margin of the sternum. The edge of the liver did not extend beyond the ribs. The patient expressed herself as feeling very well, and in a few days was allowed out of bed, when she found she could walk without breathlessness. The cardiac rate was only increased a few beats by this exercise.

28.10.16. She was seen in the O. P. room. The pulse at rest was 108 and after walking exercise was 132. She became very short of breath on exertion.



The apex beat of the heart was  $\frac{3}{4}$ " outside the nipple line and the liver extended 1" below the costal margin. Ordered digitalin gr. 1/250 t. d. s.

1.11.16. Pulse 92 on arrival; 84 after lying down. Vomiting had occurred after six tabloids were taken and they had been stopped. The cardiac action was irregular, and this, as shown by polygraph tracings, was due to sinus irregularity (respiratory variation). The apex beat was in the nipple line and the liver was not enlarged.

4.11.16. Pulse on arrival, 104; 108 after walking round O. P. room. Patient did not show any breathlessness.

11.11.16. Pulse 100 on arrival; 104 after walking round O. P. room. Has taken two tabloids.

22.11.16. Has taken four tabloids since the 15th. Pulse at rest, 96; 112 after walking round O. P. room. Patient has been very well.

21.2.17. Condition satisfactory. Has been taking tabloids occasionally for breathlessness.

28.3.17. Pulse-rate 96. Has been attending school.

18.6.18. Seen as out-patient. Is now  $12\frac{1}{2}$  years old. She has been attending school regularly and has had no rheumatic trouble or other illness. She can walk quite well, but after a run of any distance her heart beats very fast. The cardiac action is of normal rhythm and the rate is 84 per minute, quite regular. The pulse is of good volume and tension. There is a marked heaving thrust at the apex, which is  $\frac{3}{4}$ " outside the nipple line. At the apex there is a loud systolic murmur (mitral) and at the base a well-marked diastolic murmur, heard after exercise, and evidently aortic in origin. The nutrition, colour, and spirits are very good.

*Case III. E. B., female,  $12\frac{1}{2}$  years. Rheumatic carditis. Mitral obstruction. Dilatation and hypertrophy of right heart. Cardiac failure with rapid action. Slowing of heart rate by digitalis. Effect of digitalis on heart rate after exercise, excitement, &c.*

This patient was first seen in the beginning of 1916, at the age of ten years, when she complained of pain in the left side of the chest and palpitation. There was dilatation and hypertrophy of the right side of the heart and a well-marked presystolic thrill and murmur at the apex. The action of the heart was regular and the rate 72–80 per minute. Breathlessness was induced by active exercise. She was very liable to attacks of tonsillitis and pains about the extremities.

In the following year (20.6.17) she was admitted to hospital suffering from cough, breathlessness, and some oedema of the face. There were coarse râles over the lower lobe of the right lung. The acute symptoms subsided in a few days. The cardiac hypertrophy of the right side had increased and there was marked heaving of the chest wall at and on both sides of the sternum. There was no dilatation of the left ventricle. The presystolic thrill and murmur persisted. The pulse was regular, small, and weak, and the rate was usually 80 per minute. A note was made of the extreme facility with which the pulse-rate ran up to 120 or 130 on any excitement or emotional disturbance. She was discharged and sent to a home in the country, where she remained for eight months.

She was readmitted (20.2.18) with marked signs of cardiac failure, general oedema, oedema of lungs, breathlessness at rest, enlarged liver, oliguria, and albuminuria. These conditions had been present for ten days, and had come on without any known exciting cause. The cardiac action was rapid—130 per minute and regular. There was great dilatation of the right side of the heart and the apex beat was  $\frac{1}{2}$ " outside the nipple line. A loud systolic murmur was heard all over the præcordia and in the axilla, but no presystolic thrill or murmur could be made out. The symptoms being urgent, digitalis was begun at once. (See Table I.)

TABLE I.

Date.	Doses of Digitalin gr. 1/240.	Pulse-rate.	(Ounces) Urine.	Remarks.
Feb. 20	2	130	—	General oedema, liver enlarged, pulmonary oedema, dyspnoea
21	4	130	19	Dilated right heart. Albuminuria
22	2	116	14	Vomited once (? cause)
23	—	120	20	Oedema less. Dyspnoea less
24	2	124	20	
25	4	112	19	
26	1	68	40	Vomited once. (Note urine)
27	—	72	21	Feels well. Oedema and congestion gone. Heart less dilated
28	—	96	20	
Mar. 1	1	110	22	Transient pyrexia (100.6°)
2	1	96	27	
3	1	100	33	
4	1	100	27	
5	1	96	20	
6	2	108	23	Tracings show normal rhythm
7	1	96	26	Vomited once
8	—	96	28	
9	—	96	22	
10	—	100	19	
11	—	112	21	
12	—	100	29	Patient allowed up
13	—	96	28	
14	—	96	28	
15	—	88	28	
16	—	88	29	

On the third day the patient vomited and the digitalin was stopped as per instructions. As there was no pronounced change in the cardiac rate, the vomiting was regarded as accidental (not from digitalis) and the drug was resumed. After the fifteenth dose the patient vomited and the pulse-rate fell to 68 per minute. Coincidentally the amount of urine passed in twenty-four hours rose to 40 ounces, which was double the amount passed on any previous day. There had been a slight improvement as regards the oedema from the rest in bed but a most marked effect following the slowing—both external oedema and internal congestion disappearing. The dilatation of the right heart was considerably lessened. The presence of the presystolic murmur was not noted until a week after the definite slowing, and its absence previously was ascribed to the rapid and weak action of the auricle. A regular action of the heart had persisted throughout.

Three weeks after the last dose of digitalin had been given the heart action again began to be too rapid and too easily excited to increased rate. For example, the pulse at rest was 108, and when the patient sat up in bed three times it rose at once to 120. At the same time the breathlessness on exertion increased and the liver was enlarged. Another course of digitalin was given.

When slowing occurred the general and local conditions were much improved. The slowing after this course was pronounced and persistent. The heart for some days continued beating regularly at from 48 to 52 per minute. Tracings taken showed a normal rhythm. (See Table II.)

Some tests were made as to the effect of muscular movements on the cardiac rate. After sitting up in bed three times the pulse rose from 52 to 56, a very slight increase. A few days later the pulse-rate at rest was 88; after the patient sat up in bed four times, it rose to 100; after she walked quickly round the ward it was 116, and the respirations were 20 per minute. These increases in rate were very much less than those which had been noted under similar tests when the heart was not controlled by digitalis. Reference has been made to the

excitable and emotional temperament of this patient, and the effect of this on the pulse. Under ordinary conditions an examination by the doctor would at once increase considerably the cardiac rate, an increase which would last for some time. When, however, the heart was controlled by digitalis the doctor's examination showed a heart rate undisturbed and identical with that recorded

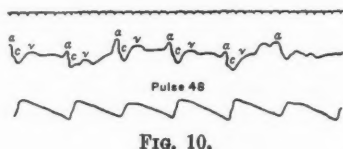
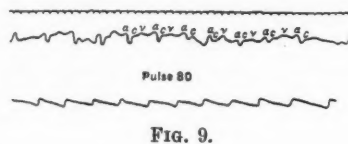
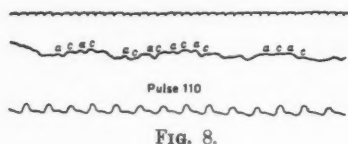


TABLE II.

Date.	Doses of Digitalin gr. 1/250	Pulse-rate.	Remarks.
Mar. 27	—	108	After sitting up three times P. = 120
28	—	100	
29	—	112	
30	—	110	
31	—	100	
Apr. 1	—	108	(Last dose of digitalis was on March 7) Cardiac dullness 1½" to right of sternum. Liver considerably enlarged. After sitting up four times P. = 116
2	1	108	
3	2	110	
4	2	80	Vomited twice. Pulse tracings show a normal regular rhythm. Colour good, breathing easy. Liver not enlarged Vomited once
5	1	52	
6	—	56	
7	—	56	Allowed out of bed
8	—	52	
9	—	52	
10	—	52	
11	—	92	
12	—	88	After sitting up in bed four times P. = 100. After walking briskly round the ward P. = 116. R. = 20
13	—	72	
14	—	84	
15	—	80	
16	—	80	

by the ward Sister at quiet intervals of the day. These findings were confirmed later in the out-patients' room. Under ordinary conditions she would have on entrance a cardiac rate of 116 to 124, but under moderate doses of digitalis the records were on consecutive visits 104, 92, 100, 96, and these rates were considerably reduced before the end of the visit.

She continued taking ten minims of the tincture of digitalis daily for a month, and during this time the pulse-rate remained regular and steady between 80 and 90 per minute. There was always dyspnoea on active exertion,

but she was able to get about comfortably. The liver was not enlarged and there was no oedema. During the following month she had no digitalis and again the signs and symptoms of cardiac failure became pronounced, and she was readmitted to hospital. It was stated that for a week she had been complaining of pains about the arms and legs, and that her face became puffy. For the previous three days she had had great difficulty in breathing, could not lie down in bed, had been very blue, and had had swelling of the face and extremities. On admission there were all the signs of cardiac failure, namely cyanosis and orthopnoea, pulmonary oedema, enlarged liver, and subcutaneous oedema. The cardiac rate was 127 per minute and regular. The heart was much enlarged, with great over-action of the right side. The temperature was subnormal.

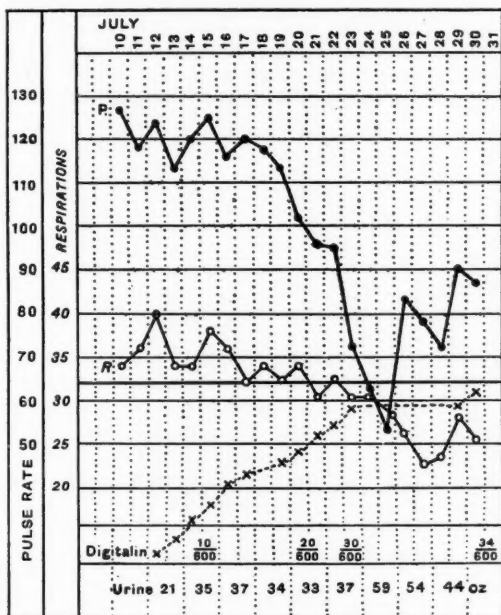


Fig. 11.

The chart (Fig. 11) shows the effect of digitalin treatment on the pulse and respiration rates, and on the amount of urine passed. She was given at first a daily hypodermic injection of digitalin (gr. 1/260) for four days without any definite effect. She was then ordered digitalin (gr. 1/300) by the mouth, and when she had received in all gr. 1/30 of digitalin the pulse had fallen to 96 and the respirations to 30. When she had taken gr. 1/20 digitalin the pulse-rate had fallen to between 60 and 70. Relief to the symptoms of distress and to the visceral congestion, which had been progressive with the fall in the pulse-rate, was now completely secured, and two days later she was allowed out of bed at her own request. When the pulse-rate rose to between 80 and 90 the digitalin was resumed in smaller doses.

The cardiac lesion in this case is undoubtedly progressive. In the first place she has at times rheumatic pains in the limbs, with slight pyrexia, which indicate that the infection is active at times. This can be controlled by salicylate of soda, but at the same time a fresh infection of the myocardium may be going on. In the second place the mitral stenosis has led to great dilatation of the

auricles and the right ventricle and to a permanent limitation of the cardiac power, as shown by breathlessness on exertion, even when the heart is beating at rest at the normal rate. If prophecy were called for one might say she was in a condition in which auricular fibrillation might develop at any time. In order to stave this off the best treatment will be to keep the heart rate steady with ten or fifteen minims of tincture of digitalis daily, and to continue this probably for the remainder of her life.

*Case IV. E. W., female, 5 $\frac{1}{2}$  years. Rheumatic fever. Carditis. Mitral regurgitation and dilatation. Cardiac dyspnoea. Rapid cardiac rate with normal rhythm. Digitalis slowing and marked benefit.*

June 1917. About four months previously patient had her first attack of acute rheumatism, for which she was kept in bed at home for three months. During the past month she had been up and going about, but had had no energy and had never wanted to take any exercise. She had been very short of breath on exertion, and complained frequently of pains in the legs and at the praecordium.

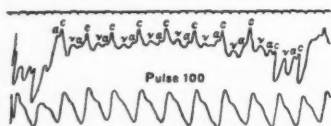


FIG. 12.

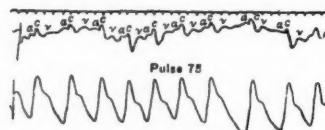


FIG. 13.

On admission the temperature was normal and the pulse was persistently rapid but regular. During rest there was considerable overaction of the respiratory muscles, and any exertion brought on great dyspnoea, with an increased cardiac rate. The apex beat was  $\frac{1}{2}$  inch outside the nipple line; the right side of the heart was not enlarged. At the apex there was a loud systolic murmur, apparently mitral in origin, and audible all over the praecordium and in the axilla. The liver was enlarged, extending two inches below the ribs in the nipple line.

After full doses of digitalin the cardiac rate was slowed, and this action was maintained by occasional small doses of the drug. The patient's general condition and comfort were much improved and she was soon able to be up and about without discomfort. (For details see opposite page.)

She was seen again six weeks after leaving the hospital. The treatment had not been continued. The cardiac rate was 124 and regular. The liver extended two inches below the costal margin. The breathing was distressed on making any exertion and she could take but little exercise. The cardiac condition was as above described. She was ordered digitalin, gr. 1/250, every second or third day. This treatment was again followed by improvement, and slowing of the heart.

22.8.17. P. = 100, regular. Walking much better, less breathlessness.

5.9.17. P. = 100, regular.

12.9.17. P. = 96, regular.

It was found possible to keep the excessive cardiac rate in check by means of digitalis. She did well and returned to school, but had a fresh attack of rheumatism in December. In the following March she was seen. She had been attending school and took moderate exercise without dyspnoea. The cardiac rate was 100 per minute. The liver was not enlarged. There was no change in the physical signs about the heart, evidences of mitral regurgitation without much ventricular dilatation being still present. The previous condition of a persistently rapid cardiac rate had entirely ceased.

Date.	Doses of Digitalin gr. 1/240.	Pulse-rate.	Remarks.
June 6	—	104	Cardiac action regular
7	—	120	
8	2	124	
9	3	110	Vomited once
10	—	124 (M.), 100 (E.)	Vomited twice
11	—	88	Pulse irregular. Tracings showed a normal sinus rhythm with respiratory irregularity only
12	1	80	
13	1	88	
14	1	76	
15	1	80	Edge of liver at costal margin
16	—	90	Vomited once. Up in a chair
17	—	76	Walking about. No discomfort or dyspnoea
18	1	74	
19	1	80	
20	1	96	
21	1	76	Vomited once
22	—	84	Vomited once
23	—	108	
24	—	100	
25	—	88	
26	—	84	
27	—	100	
28	—	80	
29	—	84	Pulse good volume and tension. Patient going about. No symptoms of discomfort
30	—	88	
July 1	—	80	
2	—	88	
3	—	80	
4	—	88	

Case V. E. H., female, 5 years. Acute rheumatism. Arthritis. Erythema. Rheumatic nodules. Mitral regurgitation. Dyspnoea. Rapid heart rate with normal rhythm. Digitalis slowing and marked benefit for a time.

This patient was admitted with a history of pain in and swelling of the ankles for some days. There was no definite history of previous rheumatic infection.

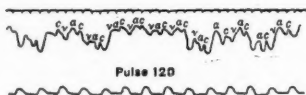


FIG. 14.



FIG. 15.

The ankles were swollen and tender and the skin over them was oedematous. There were rheumatic nodules on the knees and elbows, and a blotchy erythema over the skin of the trunk. The cardiac rate was rapid and regular. The apex beat was  $\frac{3}{4}$  inch outside the nipple and a systolic murmur there seemed due to mitral regurgitation. The liver was enlarged, extending in the mid-line to one inch above the umbilicus. The patient showed dyspnoea on making any exertion, and the lips were rather cyanosed.

She was treated with salicylate of soda, and in three days the temperature had fallen to normal and the arthritic signs had disappeared, but the cardiac rate continued rapid.



Date.	Doses of Digitalin gr. 1/600.	Pulse-rate.	Respiration.	Remarks.
Mar. 9	—	120	28	Temperature normal. No signs of acute rheumatism. Dyspnoea on making any movement. Cardiac action regular
10	—	120	28	
11	—	124	26	
12	—	122	24	
13	—	122	36	
14	—	130	32	
15	—	128	32	
16	3	120	28	
17	6	120	28	
18	6	84	24	Vomited in evening. Tracings show a normal sinus rhythm, with occasional extra-systole. Liver much diminished in size, edge palpable at costal margin
19	—	80	28	
20	—	90	24	
21	—	84	24	Patient sitting up in bed. No dyspnoea. Patient's spirits good
22	—	100	22	
23	—	104	24	
24	—	100	28	
25	—	104	28	

The administration of digitalin led to a slowing of the heart and definite improvement in the patient's condition. She continued to do well for a fortnight and was able to be up in a chair. At the end of that time she had a fresh outbreak of rheumatic infection with pyrexia, erythema, and many rheumatic nodules. There quickly supervened cardiac dilatation, rapid cardiac action, and dyspnoea, with enlargement of the liver. She was taken home by her parents against advice.

*Case VI. E. W., female, 10½ years. Acute rheumatism. Mitral disease. Pericarditis. Rheumatic nodules. Cardiac hypertrophy. Rapid, regular heart rate. Cardiac dyspnoea. Slowing of rate and relief of dyspnoea by digitalis.*

In January 1917 she had an attack of tonsillitis; in February acute rheumatism, with mitral disease and later pericarditis. Given digitalis in February to slow the heart, but without effect. She was sent to hospital in April for further treatment.

18.4.17. The child is thin and pale and gets short of breath on any exertion (e.g. walking into the hospital). No rise of temperature, no pains. Several small subcutaneous (rheumatic) nodules on elbows and knees. Hypertrophied (heaving) action of chest-wall in cardiac area. Apex beat two-thirds of an inch outside the nipple line. Right side of heart also enlarged. Loud systolic murmur at apex, transmitted into the axilla and back. The pulse is small, weak, and rapid. The liver is not enlarged. There is no oedema. Dyspnoea is present while the child is lying quietly in bed.

There was no change in the size of the heart after treatment, or in the mitral murmur. In the absence of oedema, oliguria, and enlargement of the liver before treatment there was no effect from digitalis as regards these conditions. The cardiac rate was slowed and the dyspnoea was relieved, while the patient was able to be up and take exercise without discomfort. (Progress table, p. 205.)

18.7.17. Seen as O. P. She was short of breath on any exertion, and even when lying down the breathing was distressed. The cardiac rate was 124 per minute. There was heaving action of the whole præcordia with dilatation of both sides of the heart. Evidences of mitral regurgitation were present. The liver was not enlarged. The condition was much the same as on admission to

hospital. She was ordered digitalin, gr. 1/250 (B. W. & Co.), one tabloid twice daily.

25.7.17. Patient was sick yesterday. P. = 104, regular. Breathing easier.

18.8.17. Breathing much easier. P. = 100, regular.

30.8.17. P. = 108, regular.

11.9.17. P. = 92, regular.

Date.	Doses of Digitalin gr. 1/240.	Pulse-rate.	Respiration.	Remarks.
Apr. 18	—	120	30	Kept in bed. Cardiac action regular
19	—	124	32	
20	3	128	40	
21	3	114	40	
22	3	112	38	
23	3	108	26	
24	3	100	26	
25	3	102	24	
26	3	104	24	
27	—	85	24	Vomited three times
28	—	96	24	
29	—	96	22	
30	—	88	22	
May 1	—	98	22	
2	1	92	24	Up in a chair
3	1	84	24	Walked a little
4	1	84	24	
5	1	86	22	
6	1	86	24	
7	1	86	22	Pulse 84 before exercise; 108 after walking round the ward. No dyspnoea
8	1	88	24	
9	1	100	24	
10	1	88	24	No dyspnoea when up and walking about
11	1	88	24	
12	1	84	24	

She had been taking the digitalin as required, and the breathing was much easier, as tested especially on climbing the stairs at home. The tendency to increased cardiac rate had been checked.

*Case VII. L. D., female, aged 8 years. Recurrent chorea. No history of rheumatic fever. Cardiac dilatation. Mitral regurgitation. Rapid regular cardiac action. Slowing effect produced by digitalis.*

16.2.17. Three years ago patient had an attack of chorea. She has never been treated for rheumatism. Six weeks ago the chorea recurred, with headache, screaming, and irritability.

She is now very dull and apathetic; is unable to articulate or feed herself. There is extreme emaciation. The heart is dilated, the apex beat being  $1\frac{1}{2}$  inches outside the nipple line. The action was regular and rapid, 124 per minute. There was a loud systolic murmur at the apex, conducted well into the axilla. The liver was not enlarged, there was no dyspnoea, and the temperature was normal.

The following table shows the progress of the case and the effect of digitalis in slowing the heart. When the effect of the first course of digitalis had passed off, and the cardiac rate again increased, the employment of small doses regularly again reduced the rate and kept it under control.

Date.	Doses of Digitalin gr. 1/240.	Pulse-rate.	Respiration.	Remarks.
Feb. 16	—	124	32	Active choreic movements under observation. Cardiac action regular
17	3	136	28	
18	4	128	28	
19	2	88	26	
20	—	64	22	Polygraph tracings show normal sinus rhythm
21	—	80	22	
22	—	60	22	Child quieter, and able to phonate. Cardiac action irregular, owing to extra-systoles and respiratory irregularity
23	—	68	22	
24	—	88	22	No extra-systoles present
25	—	80	22	
26	—	80	—	Apex beat one inch to left of nipple line. Restlessness gone. Child looks much more healthy
27	—	100		
28	—	112		
Mar. 1	1	100		
2	—	100		
3	1	102		
4	—	96		
5	1	100		
6	—	102		
7	1	118		
8	—	100		
9	1	100		
10	—	100		
11	1	102		
12	—	80		
13	1	88		
14	—	88		
15	1	80		
16	—	80		
17	1	88		
18	—	80		
19	1	90	—	Patient quite happy and cheerful
20	—	84		
21	—	100		
22	—	96	—	Developed measles and sent to fever hospital

*Case VIII. A. F., female, 7 years. Rheumatic carditis. Mitral regurgitation with dilatation and hypertrophy of the left ventricle. Rheumatic nodules. Praecordial pain. Regular rapid cardiac action. Slowing of heart by digitalis.*

Admitted to hospital, 27.2.18. The patient had been complaining recently of pain across the chest, of feeling her heart beating quickly, and of increasing shortness of breath. A year previously the school doctor had found that her heart was affected. She had suffered from pain and swelling in the hands and feet, but had never been laid up with rheumatic fever.

There was dilatation and hypertrophy of the left ventricle. At the apex a ringing first sound was followed by a musical systolic murmur which persisted through the whole of the systole. The murmur was heard well out in the axilla and also over the whole praecordia. The liver was not enlarged. There was no dyspnoea while the patient was at rest. Rheumatic nodules were present on the knees and elbows. The cardiac rate was persistently rapid, usually about 120 per minute, and the action was regular. The temperature was normal, and remained so for the six weeks she was in hospital, with the exception of a slight rise (99°) occasionally.

The effect of digitalis in this case was to slow the cardiac action, and to slow it permanently as regards the time she was in hospital. The patient was

Date.	Doses of Digitalin.	Pulse-rate.	Remarks.
Mar. 9	—	120	Kept in bed
10	—	124	
11	—	120	Tracings show normal rhythm
12	—	118	
13	—	112	
14	—	120	
15	2	120	Digitalin gr. 1/240 (Nativelle) begun
16	3	116	
17	1	112	Digitalin stopped as supply gave out
18	—	120	
19	2	100	Digitalin gr. 1/250 (B. W. & Co.)
20	—	80	Vomited three times
21	—	96	Vomited once
22	—	64	
23	—	80	
24	—	68	
25	—	68	
26	—	96	Slight rise of temperature
27	—	88	
28	—	88	
29	—	80	
30	—	68	Patient allowed to take walking exercise
31	—	80	
Apr. 1	—	96	
2	—	72	After sitting up in bed four times quickly P. = 72. On repeating it P. = 80
3	—	80	
4	—	80	
5	—	68	No shortness of breath after exercise
6	—	84	
7	—	92	Tracings show normal rhythm
8	—	84	After sitting up quickly four times P. = 84
9	—	90	
10	—	86	
11	—	88	

much relieved as regards the breathing. Observations were made on the effect of muscular exertion on the heart rate when it was still definitely under the influence of digitalis. Slight exercises in bed had very little effect in increasing the heart rate.

*Case IX. C. D., male, 10 years. Rheumatic infection. Endocarditis. Subcutaneous nodules. Later, definite signs of cardiac failure, with rapid regular action of the heart. Slowing action of digitalis with relief of symptoms.*

This boy had been in the hospital at the age of 8 years, suffering from rheumatism and heart trouble. The apex beat was then in the nipple line and there was a systolic murmur following the first sound. The rate was increased for a few days during the pyrexial stage, which yielded to salicylate of soda. Thereafter the heart rate dropped to 80 and continued at that rate during his stay in hospital, the action throughout being regular. There were subcutaneous nodules on both elbows. There was no dyspnoea, or enlargement of the liver, or pulmonary oedema. He remained in hospital for three weeks and during that time showed no evidence of cardiac weakness, so far as symptoms were concerned.

Two years later, at the age of 10 years, he was admitted with marked signs of cardiac failure. He had been breathless on exertion for some time, often became very blue, and a week previously the face and lower extremities had swelled. Coughing had been troublesome and vomiting had come on. On admission the temperature was normal, the pulse-rate 120, and the respiratory rate was 36.

He was cyanotic and the breathing was laboured (orthopnoea). There were many crepitations scattered over both lungs, while the note over the left lower lobe was dull and bronchial breathing was present there (collapsed lung from cardiac pressure). The extremities were oedematous and the liver was considerably enlarged and very hard. The heart was enlarged on both sides. The impulse was feeble and the action was regular and rapid. A systolic murmur, audible over the praecordia and in the axilla, followed a rather accentuated first sound, and a diastolic murmur was occasionally present at the apex. During the following three weeks his condition varied from time to time, but there was no real improvement. Coughing was very frequent and disturbed him day and night. Pain over the liver region was complained of and leeching was tried there without any relief to the pain or the hepatic enlargement. Tincture of digitalis was given from the start, at first twelve minims daily and later fifteen. This had to be intermitted at times because of vomiting, but it produced no effect as regards the patient's condition. It was decided to try larger doses and to use digitalin.

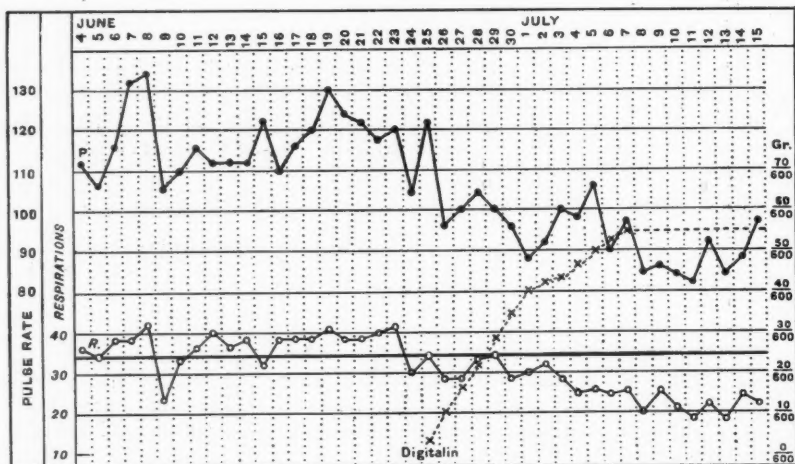


FIG. 16.

The chart (Fig. 16) represents a period of six weeks, the first half showing the pulse and respiration rates under small doses of tincture of digitalis, and the second half the effect of digitalin on these rates. In the first three weeks there was no appreciable change. In the second half both pulse and respiration rates were brought to the normal under the influence of digitalin. The treatment is charted in terms of doses of  $1/600$  grain of digitalin and the dosage and duration of treatment are shown. On the sixth day after treatment was begun the pulse was 90, the respirations were 30, and the amount of digitalin taken was  $1/15$  gr. ( $40/600$ ). The patient was relieved to a certain extent, but it was not considered that the full effect of digitalin had been obtained. The drug was continued in smaller doses for another six days, during which  $1/40$  gr. ( $15/600$ ) was taken. The pulse-rate then dropped to between 80 and 90 and the respiration rate to 20. Signs of improvement were then clearly shown and were progressive until great relief was obtained. The coughing ceased, the pulmonary oedema passed off, and the hard, swollen liver became smaller until finally it was normal in size. The breathing was relieved and the boy was able to sleep comfortably and lying down with only one pillow. Three weeks after the digitalin treatment was

begun he was allowed out of bed. No tracings were taken in this case, but clinically the cardiac action was always regular. After the cessation of the course of digitalin the cardiac rate continued under 100 for thirteen days, and then digitalin was resumed in smaller doses. There was very little diminution in the size of the heart under the slower rate, but a late diastolic murmur became more pronounced, which confirmed the opinion formed earlier that mitral obstruction was present as well as mitral regurgitation. The cardiac condition was such that any persistent increase of rate would certainly lead to cardiac failure, and this could only be avoided by the regular use of a sufficient amount of digitalis.

He became an out-patient, and continued to take a moderate amount of walking exercise without distress.

*Case X. N. B., female, 9½ years. Rheumatic fever. Endocarditis. Rheumatic nodules. Rapid and regular action of heart controlled by digitalis.*

27.8.17. A month before admission this patient had had an attack of rheumatic fever, with pyrexia and multiple arthritis, and pains in the limbs and joints. The finger-joints were still painful and swollen. There was no history of previous tonsillitis or chorea, but the presence of numerous rheumatic nodules on the knuckles, knees, elbows, and scapulae suggested that the rheumatic infection had been of longer duration than one month. The heart was enlarged and the impulse was heaving, suggesting hypertrophy of the left side. The apex beat was 1½" outside the nipple line, while the right border of the heart extended ½" beyond the sternum. There was a systolic murmur at the apex, replacing the first sound, and well heard over the praecordia and in the axilla. No evidence of aortic disease. The rate of the heart was 112 and the action was regular. There were no signs of cardiac distress while the patient was resting.

Under treatment by salicylate of soda the pyrexia and arthritic trouble passed off entirely. At the end of six weeks she was comfortable and the heart was smaller than on admission, but the rate had increased and was usually about 120 per minute, while quite regular. Digitalin was ordered in doses of gr. 1/300 thrice daily. After eight doses the patient vomited and the medicine was stopped. The pulse-rate was then 95 and it continued to fall for a few days. A rise in the pulse-rate was coincident with a slight pyrexial attack. When this subsided the digitalin was resumed, the dose being gr. 1/300 once daily. This was continued for three weeks and the cardiac rate remained under 100, the average being about 90. During this time she was allowed out of bed and to take graduated exercises. After these at first the pulse-rate was quickened and rose to 104 and dyspnoea was present. Later, after walking about the ward, there was no marked increase of the pulse-rate and no dyspnoea. The cardiac condition remained practically unchanged, the dilatation and hypertrophy of the left ventricle associated with mitral regurgitation being somewhat less than on admission.

19.6.18. Seven months later she was readmitted to hospital. Up to two months previously she had been able to get about comfortably, although short of breath on much exertion. At that date she had suffered from pain and swelling in the knees and ankles. The breathing had become laboured even at rest. She had been compelled to lead a very quiet life, usually remaining in bed for two or three days in the week, and getting up about midday on other days. She could not walk any distance owing to shortness of breath and exhaustion.

On admission the patient's breathing was very rapid and distressed, but it quieted down considerably with rest. The condition of the heart as regards



size and murmurs was practically unchanged as compared with that on her former visit. The cardiac action was rapid, 124, and regular. There was slight oedema of the ankles, the liver was enlarged, and many subcutaneous nodules were present.

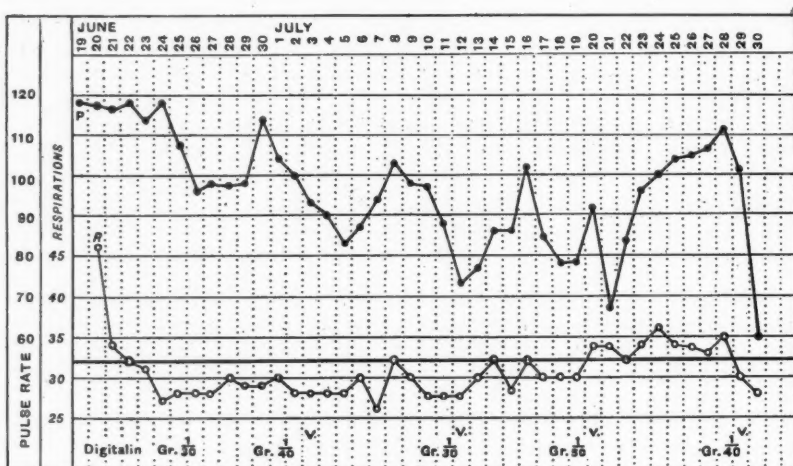


FIG. 17.

The accompanying chart covers a period of six weeks and shows the effect of digitalin on the heart rate. There were in all five courses of digitalin, and each one was followed by a fall in the pulse-rate. Although the amount of digitalin in each course, as indicated, was considerable, the fall in the number of beats was by no means striking. This also had been noted in the course of treatment in the previous year. Another point to be noted was that after each course of digitalin was stopped the pulse-rate tended to rise in a few days. This indicated that a continued effect from digitalin was not easily secured, probably as the result of continued rheumatic infection. This rapid escape of the heart from the controlling effect of digitalin was also noted at her previous visit. The interrupted administration of digitalin was due to the onset of vomiting (marked V in chart, Fig. 17), which, along with the large amount of digitalin given, was taken to indicate the advisability of discontinuing the drug. The total amount of digitalin given in the five courses, namely  $\frac{1}{4}$  of a grain, was considerably larger than is usually required for a child of eight or nine years, but at the same time the total duration of the treatment was considerably longer than usual. It was further noted that the respirations never became slow and without any over-action of the respiratory muscles. From this it was concluded that under the most favourable conditions, for example with a normal rate of pulse, the cardiac efficiency had been so impaired by myocardial and valvular changes that the pulmonary circulation was carried on with difficulty. It has been noted in other cases that a fall in the pulse-rate under digitalis was accompanied by a fall in the respiration rate, provided that the respiratory trouble was due to the effect of the rapid cardiac rate on the heart's action, and was not due to the primary and permanent cardiac lesions. After one course of digitalin, the onset of vomiting (on the 12th) was followed for some hours by a very slow and irregular pulse. The rate fell to 56, and the irregularity was of the phasic variety associated with digitalis, as shown by a pulse-tracing. For the most part the

slowing took place without any disturbance of the cardiac regularity, as shown on the accompanying tracings (Figs. 19, 20).

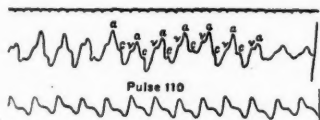


FIG. 18.

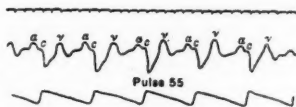


FIG. 19.

At the end of the charted period the pulse-rate had fallen to 60, and it continued under 80 for the following four days. After that it was maintained at a rate of between 80 and 90 by occasional doses of digitalin. The objective signs of cardiac failure (oedema, enlargement of the liver) had all passed off with the slowing of the cardiac rate, but she was able to take only a limited amount of exercise owing to the dyspnoea induced.

# ACUTE LEUKAEMIA AND SO-CALLED MEDIASTINAL 'LEUKOSARCOMATOSIS' (STERNBERG)

WITH THE ACCOUNT OF A CASE ACCOMPANIED BY MYELOID  
·SUBSTITUTION OF THE HILUS-FAT OF THE KIDNEYS

By F. PARKES WEBER

With Plates 13-15

AMONGST the various cases of leukaemia in which definite localized nodules or masses of leukaemic infiltration develop in the skin, subcutaneous tissue, periosteum, and in various parts of the body (Gordon Ward suggests 'nodular leukaemia' as a convenient term for such cases (1)), a very characteristic though somewhat rare clinical and pathological group is constituted by examples of so-called mediastinal 'leukosarcomatosis' (Sternberg). In this group a dense, tumour-like mass occurs in the mediastinum, generally at the base of the heart and apparently growing from the thymus gland, remnants of which may sometimes be found in the growth. The tumour-like growth tends to spread downwards over the pericardial sac and to envelop it 'like a blanket'.

The term 'leucosarcoma' was introduced by C. Sternberg (2), about 1905, for growths of this pathological type, including chloroma and mediastinal leucosarcoma. They were, or had been, apparently regarded as a kind of sarcoma made up of white 'lymphoid' cells which were constantly being thrown off into the blood-stream, thus giving rise to a leukaemic blood-picture in the circulating blood. These 'lymphoid' cells were large non-granular uninuclear cells, more or less resembling large leucocytes, and though in some cases they might really belong to the lymphocytic series of blood-corpuscles and represent a 'pre-lymphocyte' or 'lymphoblast' stage, they might in other cases (and I now believe that they do in most cases) belong to the myeloid series and represent a non-granular 'pre-myelocyte' or so-called 'myeloblast' stage, often giving a positive oxydase reaction.

Thus, cases of 'leukosarcoma' and chloroma ('chlorosarcoma') were by some authorities, from the pathological point of view, supposed to constitute connecting links between the various kinds of sarcoma on the one hand and the various kinds of leukaemia on the other hand.

Most cases of mediastinal 'leukosarcomatosis' have not been recognized as

such until the post-mortem examination. The first case that I met with (Case I, see below) was regarded as merely one of acute leukaemia until the necropsy revealed the remarkable tumour-like mediastinal mass, including the remnant of the thymus gland, and enveloping a large portion of the pericardial sac. The recent case of a boy is, however, described (Case VI), in which I was able by the help of Röntgen-ray examination and by the microscopical blood-picture to make the diagnosis *intra vitam*. The boy was admitted to hospital with fever, respiratory distress, and ascites, and was at first supposed to be suffering from tuberculosis. However, his extreme pallor and the presence of cutaneous petechiae suggested an examination of the blood, which revealed the leukaemic blood-picture. Owing partly to his peculiar dyspnoea a Röntgen skiagram of the thorax was taken, and this showed great shadowing at the base of the heart, suggesting the presence of a tumour-like mass in the mediastinum.

I shall now proceed to give details of some (with one exception) typical cases.

*Case I.* The patient (3) was a clerk, aged 18 years, admitted to hospital on March 21, 1914, said to have been ailing for the last month and to have suffered from pains in the right side. His superficial lymphatic glands on both sides of the neck, in both axillae, and in both groins were moderately enlarged, and so were his tonsils. His spleen, which felt hard, extended downward to just below the umbilical level, and the liver was likewise somewhat enlarged. There was slight pyrexia of an irregular type. The urine was free from albumin. There was a moderate pleural effusion on the right side, and 800 c.c. of this fluid were aspirated on March 25; its specific gravity was 1.008; clear; slightly red from admixture of blood. A blood-count on March 23 proved the case to be one of leukaemia; the white cells were estimated at 131,000 to the cubic millimetre of blood. Treatment by the application of Röntgen rays and the internal use of arsenic was commenced soon after the patient's admission, but the Röntgen-ray therapy was discontinued after the first séance, and the case ran the invariably fatal course of acute or subacute leukaemia. In the second half of April it was obvious that the patient was going downhill and rapidly losing strength. There had been much epistaxis. There were purpuric spots (petechiae) on the legs and retinal haemorrhages in both eyes. Since admission there had often been slight pyrexia (up to 100° F.). The lower extremities became oedematous and the petechiae gradually increased in number; dark ecchymoses appeared spontaneously about both eyes. In the latter part of April the faeces were fluid and coloured red with blood. The spleen diminished somewhat in size towards the end. Death occurred on May 5, 1914, 6½ weeks after admission.

The last blood-count (April 26) had given 1,500,000 red cells and 176,000 white cells to the cubic millimetre of blood. Nearly all the white cells belonged to the large non-granular uninuclear class. No nucleated red cells were seen on that occasion, but a few had been noted on March 31, when the differential count of white cells showed that only 2 per cent. were polymorphonuclear neutrophils. Dr. Gordon Ward, who kindly examined some blood-films taken on April 27, thought that the large uninuclear cells were precursors of the ordinary lymphocyte type, and he could find no nucleated red cells and no granular myelocytes such as one might expect to be present in any myeloid leukaemia.

The *post-mortem examination* showed a hard, white, tumour-like mass in the superior mediastinum, apparently originating at the site of, and enclosing the remains of, the thymus gland. It spread downward over the parietal pericardium, almost the whole of which it enclosed 'like a blanket'. There was some pleural effusion on the right side. The heart (weight 11 ounces), lungs, and aorta showed nothing special. The spleen was enlarged, weighing 27½ ounces and

measuring  $18 \times 12 \times 6$  cm. It was of rather hard consistence and contained several anaemic infarcts (doubtless of leukaemic thrombotic origin), and its substance, excepting the infarcts, was of a dark crimson colour. There were several perisplenic adhesions. The liver was enlarged, weighing 80 ounces, but on section by naked-eye examination it appeared normal. The kidneys, weighing together 13 ounces, were pale. Nothing special was noted in the pancreas, alimentary canal, or thyroid gland. The brain and spinal cord were not examined. The lymphatic glands were moderately enlarged throughout; many of them were white, others were reddish; among the latter were some of the mesenteric and some of the cervical glands. The right humerus was sawn open longitudinally and the marrow in the shaft was found to be of a bright red colour.

A *microscopical examination* was made of various parts of the mediastinal tumour-like mass, of a cervical lymphatic gland, of bone-marrow, and of the spleen, liver, and a kidney. Summing up the results, it may be said that all the tissues examined were permeated with a kind of lymphoid cell, the mediastinal 'tumour' being perhaps merely a local exaggeration of this lymphoid permeation, connected with, and apparently growing from, the remnant of the thymus gland. The conclusion was unavoidable that the lymphoid cells which permeated the various tissues of the body were of the same kind as the lymphoid cells which, during the patient's life, constituted by far the greatest portion of the white cells in his circulating blood. I thought at the time that the cells in question were probably to be regarded as cells of the large lymphocyte class, or rather as 'lymphoblasts', the precursors of lymphocytes, but, on further consideration, from a comparison of the case with Case VI, and from the fact that, as mentioned farther on, a few of the cells gave a positive oxydase reaction, I now think that they were probably 'myeloblasts', the precursors of myelocytes. The guaiac reaction with the patient's blood (tried according to the directions given in Otto Naegeli's (4) work) gave a negative result. Dr. J. S. Dunn (5) was, however, kind enough to try the oxydase reaction in blood-films taken during life and sections of the tissues made after the patient's death. He found that the vast majority of the mononuclear (lymphoid) cells gave no oxydase reaction, but that a few did give one.

*Case II.* With the last case may be compared one described by W. Mager (6) (of Brunn) in 1909. His patient was a man, aged 21 years, with a pleural effusion (a transudate) and enlargement of the lymphatic glands in the neck and axilla on the side of the effusion. Dilated thoracic veins, subconjunctival ecchymoses, enlargement of the spleen, and dyspnoea were notable features of the clinical picture. A blood-count gave 810,000 white cells to the cubic millimetre of blood, of which 95 per cent. were large mononuclear (uninuclear) cells of the kind found in C. Sternberg's 'leukosarcoma' cases. The necropsy showed the presence of a large infiltrating tumour-like mass in the anterior mediastinum, consisting of characteristic cells of the same class. The illustration accompanying Mager's paper shows that the condition was very similar to that found in Case I. The main mass of the tumour was in the region of the thymus gland, but prolongations downward had grown over the parietal pericardium, enveloping it like a blanket.

*Case III.* Another remarkable case was reported by W. D. O'Kelly (7) in 1914. The patient was a tall, slender youth, aged 19 years. He got a severe wetting on August 13, 1913, and felt unwell after it. He then seemed weak and 'remained idle'. He was admitted to the hospital on September 19, 1913. The temperature was  $100^{\circ}$  F. The splenic dullness was somewhat increased. There was stomatitis. The blood-serum, which had a milky appearance, gave a negative Wassermann reaction for syphilis. A blood-count gave 1,472,000 red cells and 295,000 white cells to the cubic millimetre of blood; haemoglobin, 26.25 per cent. The differential count of white cells gave: polymorphonuclear neutrophils,



1.5 per cent.; neutrophil myelocytes, 0.5 per cent.; lymphocytes, 15.5 per cent.; large mononuclears, 3.5 per cent.; myeloblasts and lymphoblasts, 79 per cent. The general condition of the patient became steadily worse, though the stomatitis disappeared. His temperature ranged between 100° and 104° F. His pulse was 100 to 140 per minute, and his respiration was 24 to 36. There was slight epistaxis on October 3. Death took place on October 5, 1913. Clinically, the author pointed out, the case was one of acute leukaemia of the 'large lymphocyte' class, and the 'leukosarcomatosis' was not discovered during life. At the post-mortem examination, 'on removing the sternum a large pale pink mass, the size of a closed fist, was seen filling up the superior mediastinum. It was moulded on the pericardium and the great vessels were surrounded by it. The trachea was embedded in its posterior wall. On section it was firm, with a few necrotic areas of the size of a sixpenny piece. None of the usual thymic remnants were seen. . . . No pleural adhesions were present.' No evidences of tuberculosis were discovered. A specimen of the blood from the heart taken at the time of the necropsy yielded a pure culture of *B. coli*. Microscopic examination showed the mediastinal mass to have the structure of Sternberg's 'leukosarcomatosis.' It apparently contained no concentric corpuscles of Hassall. There was typical cellular (leukaemic) infiltration of the kidneys and liver. For further details the reader must be referred to the original paper.

*Case IV.* Another illustration of mediastinal 'leukosarcomatosis' is furnished by a specimen in the Pathological Museum of St. Bartholomew's Hospital, London, classified as 'sarcoma with lymphæmia' among 'Diseases of the Thymus and Thyroid Glands' (8). The patient, a girl, aged 5 years, who died after five weeks' illness, had a blood picture of lymphocytic leukaemia. The red cells were estimated at 2,000,000 per cubic millimetre of blood; the white cells numbered 60,000 per cubic millimetre, of which 88.5 per cent. were lymphocytes. At the necropsy the anterior mediastinum was found to be occupied by a large solid yellow growth, which lay upon the upper half of the pericardium and partially enveloped the lower two thirds of the trachea. The parietal pericardium, but not the visceral pericardium, was infiltrated. The kidneys of the patient were infiltrated with yellowish secondary deposits, consisting of small round cells.

All the above cases were characterized by the presence of acute or subacute leukaemia in association with a tumour-like mass in the superior mediastinum, spreading downwards over the pericardium.

*Case V.* This case is incomplete and uncertain. The patient, S. S., a man, aged 57 years, had, when seen by me (1915) towards the end of his illness, impairment of resonance at the base of the right lung, general bronchitic signs, and somewhat stridulous breathing. He had been ill for about 5½ months. The *necropsy* showed a large, hard, white tumour-like mass, enclosing the bifurcation of the trachea, both bronchi, the descending thoracic aorta, and (pigmented) bronchial lymphatic glands; microscopically it consisted of lymphocyte-like cells. It infiltrated the lower part of the right lung and a small portion of the left lung. By microscopical examination of the liver, periportal infiltration with similar lymphocyte-like cells was seen here and there; and there were small collections of similar cells in the cortical substance of the kidney, below the capsule.

*Case VI.* This case (to which I have already alluded in my introductory remarks) derives its chief interest (a) from the circumstance that the presence of the mediastinal tumour-like mass was recognized during life, as well as the leukaemic condition of the patient's blood; (b) from the myeloid tissue found after death in the hilus of both kidneys. The patient, M. B., was a boy, aged 7 years, who was admitted to hospital on May 11, 1918, with what were regarded



as signs of tuberculous peritonitis. The history was that on the whole he had enjoyed good health till the winter of 1917-18, when he suffered from a good deal of coughing. During the last two months previous to admission gradually increasing pallor had been observed. During the last month he had complained of pains in the feet and had sometimes had fever. The abdomen had been distended for the last few days. There was nothing special to be noted in regard to the family history.

*In the hospital* there was great pallor, together with a swollen, 'puffy' appearance of the face. There was moderate irregular fever, never exceeding 101.4° F., with tachycardia and dyspnoea. The pulse varied between 120 and 152 per minute, and the respiration between 32 and 44. The urine, at first somewhat scanty, was afterwards of average or more than average amount (up to 1,800 c.c. in the twenty-four hours); it was of specific gravity 1.012 (on the one occasion on which the specific gravity was taken), acid, free from sugar, acetone, and diacetic acid, containing a trace of albumin, but showing nothing special by microscopic examination of the centrifuge sediment.

There was moderate ascites (which tended to diminish rather than increase in degree), and the feet and lower extremities were oedematous. The liver and spleen were enlarged; the lower edge of the liver could be felt reaching down to the umbilical level, whilst palpation of the spleen showed that it extended down to the anterior superior iliac spine. There was moderate discrete enlargement of the superficial lymphatic glands in the neck, axillae, and groins. In the left eye was a retinal haemorrhage. There were some scattered cutaneous patchiae, especially on the lower extremities, and these, together with the glandular enlargement, suggested an examination of the child's blood (see farther on), which revealed the presence of (doubtless acute) myeloid (myeloblastic) leukaemia. There was considerable dullness to percussion over the upper part of the chest (sternum and adjoining parts on both sides of the sternum), and a Röntgen skiagram of the thorax (see Plate 13, Fig. 1) showed great shadowing in that region, suggesting the presence of a tumour-like mass in the upper mediastinum above the heart. It seemed to me, therefore, fairly clear that we had to do with one of those rare cases of acute leukaemia in which a condition of so-called mediastinal 'leukosarcomatosis' (Sternberg) was present. The pains complained of in the feet, and the tenderness elsewhere, might possibly have been due to the bone-marrow disease; apparent tenderness over the bones of the front of the thorax should be mentioned. A Röntgen skiagram of the feet showed the absence of secondary hypertrophic osteo-arthritis (Pierre Marie), such as sometimes occurs in cases of mediastinal disease (9).

The boy was excessively feeble and had an aphthous deposit on the fauces and pharynx. He died on May 19, 1918, eight days after admission, a trial of arsenical treatment and the subcutaneous injection of normal fresh human blood doing no good.

*Blood-count* (May 13, 1918). For the differential count I am indebted to the great kindness of Dr. Gordon R. Ward. The blood when taken looked thin and watery. Haemoglobin, 20 per cent. Red cells, 1,600,000 per cubic millimetre of blood. White cells, 103,125 per cubic millimetre of blood. Colour index, 0.625. The erythrocytes showed slight poikilocytosis and anisocytosis. Dr. Ward's differential count of 500 white cells gave polymorphonuclear neutrophils, 5.6 per cent.; myelocytes (with so-called 'neutrophil' granulations), 0.4 per cent.; myeloblasts, 94.0 per cent. Whilst counting the 500 white cells he saw five nucleated red cells, all of them normoblasts. He saw no eosinophil leucocytes, mast cells, or so-called 'transitional' leucocytes. Among the 94.4 per cent. mononuclear cells counted Dr. Ward says that there were many transition forms, but that doubtless the majority were myeloblasts; amongst the smaller cells, however, included as myeloblasts, probably some were lymphocytes. It was impossible to differentiate the lymphocytes from the cells counted as myelo-

blasts. Moreover, unfortunately, the blood-film furnished to Dr. Ward was not a quite satisfactory one.

*Necropsy and Microscopic Examination.* On opening the thorax I found a large, firm, white *tumour-like mass* occupying the mediastinum above the heart and pericardial sac, and directly behind the bony chest wall (see Fig. 2). Owing to its position it appeared to have grown from the thymus gland, but no obvious remnant of the thymus (Hassall's corpuscles, &c.) was detected in the pieces microscopically examined. Microscopic examination of three pieces showed it to consist chiefly of leukaemic cells, apparently of myeloblastic type (see farther on, in regard to the tissue at the renal hilus). In parts there were some necrotic changes present.

The heart itself weighed  $3\frac{1}{2}$  ounces and showed nothing special, excepting that at the pulmonary orifice the left and the posterior semilunar valve-segments were (doubtless congenitally) united, being separated from each other by what John Hunter termed a 'kind of fraenum or cross-bar' in his own original description of a specimen of the kind (10). Minor congenital deformities of this kind are of fairly frequent occurrence both at the pulmonary and at the aortic orifices of the heart.

The great blood-vessels of the thorax appeared normal, and so did the lungs. There were some enlarged mediastinal and bronchial lymphatic glands. There was no pleural effusion on either side. The heart and pericardial sac, together with the mediastinal growth and large vessels at the base of the heart, weighed 14 ounces. There was no evidence of any tuberculosis either in the thorax or abdomen. The thyroid gland appeared (macroscopically) normal.

On opening the peritoneal cavity there was a little ascitic effusion. The liver (weight 39 ounces) was enlarged and rather pale. Microscopically it showed typical leukaemic infiltration (chiefly interacinous) of the same myeloblastic kind. The spleen (weight 15 ounces) was much enlarged, and its rather soft red substance was studded with innumerable minute pale nodules. Microscopically it showed leukaemic infiltration with the same kind of cells, but there were likewise a few scattered cells to be seen of the bone-marrow giant-cell type (megakaryocytes). The kidneys will be described farther on. Nothing else special was noted in the abdomen. The pancreas appeared normal to macroscopic and microscopic examination. The retroperitoneal lymphatic glands were moderately enlarged, and some of the glands by the aorta were red (apparently 'haemolymph glands'). There was slight enlargement of the mesenteric and other intra-abdominal lymphatic glands. One of the axillary lymphatic glands was examined microscopically and showed leukaemic infiltration of myeloblastic (or large lymphocyte) type. Of the bones, for certain reasons, only the sternum was examined. It contained red bone-marrow, but no microscopic examination of the bone-marrow was made.

We now come to the kidneys. These were both enlarged (weight together, 10 ounces) and symmetrical in appearance. The medullary substance appeared at some parts imperfectly distinguished from the very pale cortical substance. Microscopic examination showed leukaemic infiltration with cells of myeloblastic type, as in the liver. A most striking feature of the present case was that the hilus of each kidney (that is to say, the region outside the mucous membrane of the pelvis), which is normally filled up with connective tissue and hilus-fat, was occupied by deep-red spongy tissue (see Plate 14, Fig. 3; the renal cortex was paler than here represented, when freshly cut into). Microscopic examination of this tissue (see Plates 15 and 14, Figs. 4 and 5) showed it to consist chiefly of erythrocytes (haemorrhage)—which evidently gave it its deep-red colour—and myeloid cells with large round, oval or grooved 'vesicular' nucleus, and a moderate amount of clear cytoplasm free from neutrophil and eosinophil granules (when stained with Leishman's stain)—apparently myeloblasts or 'non-granular myelocytes' (Plates 15 and 14), but some of these cells may have been lymphocytes. There were likewise

a good many cells, apparently myeloblasts, which were undergoing mitosis, their nuclei staining more deeply and showing karyokinetic figures. Scattered about were cells which I took to be erythroblasts. Here and there in some parts there were also uninuclear and multinuclear bone-marrow giant-cells (megakaryocytes) (Fig. 4). There were many areas in the hilus tissue where the original fat vesicles were more or less perfectly preserved (Fig. 5). I have to thank Mr. S. G. Shattock for his great help in regard to the microscopic examination of the case and for superintending the drawing of Fig. 5.

*Myeloid Substitution of the Tissue at the Hilus of the Kidneys.*

I regard this rare condition, when it occurs in non-leukaemic cases, as the result of a conservative vital reaction, representing an attempt on the part of the organism to supplement the haemopoietic activity of the actual bone-marrow by means of extra-medullary haemopoiesis in the tissue at the hilus of the kidneys. The change is also to be looked on as a reversion to a condition normally to some extent present during foetal life. As to the tissue at the hilus of the kidney, I prefer the expression 'myeloid substitution', or 'myeloid replacement', to the term 'myeloid transformation', or 'myeloid metamorphosis', though the myeloid tissue may perhaps be regarded as bearing a relation to the fatty tissue normally present at the kidney hilus similar to that of the red myeloid tissue in the shaft of long bones (in cases of red myeloid transformation of the yellow, fatty bone-marrow) to the yellow, fatty bone-marrow normally present.

Ivy McKenzie, C. H. Browning, and J. S. Dunn, in their short paper (1909) on 'The Occurrence of Bone Marrow in the Hilum of the Kidney in Children' (11) describe two cases. One was a child, aged 9 months, who suffered from a very advanced broncho-pneumonia of confluent character. 'The leucocytes numbered 90,000 per cubic millimetre of blood, and were mostly of an embryonic type, non-granular polymorphonuclears and non-granular mononuclears; nucleated red cells were present in considerable numbers. At the necropsy the spleen and lymphatic glands were enlarged and showed myelogenic change; the bone-marrow showed evidence of active proliferation. In the hilus of each kidney were large masses of bone-marrow tissue surrounding the vessels, and throughout the whole kidney substance there was proliferation of myelogenic tissue.' Their second case was that of a child, aged  $1\frac{1}{2}$  years, who suffered from very severe rickets. At the post-mortem examination the bone-marrow in the ribs was found to be almost entirely replaced by osteoid tissue and by the results of fibrotic proliferation. 'In the long bones there was hyperactivity of the marrow cells. The spleen was enlarged and showed evidence of myelogenic activity. The liver was normal. In the hilus of the kidney, at the point of entrance of the vessels into the organ, there were large masses of bone-marrow; there was no infiltration of the kidney substance.' According to these authors the tissue in the renal hilus in both cases showed evidence of (a) increased activity of a function that has persisted from embryonic life, or of (b) a stimulus to renewed

activity (what we may for convenience term 'activation') of a function which, in the normal course of events, goes into abeyance after birth. They state that 'an examination of fetuses ranging in age from ten weeks to nine months showed that in the hilus of the kidney there are small masses of tissue, lying round the vessels but not in the adventitia, which show evidence of haematopoietic activity. In very early embryonic life these masses are situated in close relationship with the sympathetic system and the cortical layer of the suprarenals, but they become later quite independent of these structures'.

Soon afterwards (1910) J. Fawcett and A. E. Boycott (12) recorded the case of a female child, aged 2 years, at the necropsy on whom bone-marrow was discovered in the hilus of the kidney. She had been ailing for six months before admission to hospital. The liver was moderately, and the spleen much enlarged. The blood showed 55 per cent. haemoglobin; the leucocytes numbered 31,000 to the cubic millimetre, and of these 48 per cent. were large lymphocytes, 21 per cent. were small lymphocytes, 21 per cent. were polymorphonuclear neutrophils, 6 per cent. were eosinophils, and 2 per cent. were myelocytes. At the post-mortem examination the spleen was found enlarged, weighing 101 grm., with the lymph follicles (Malpighian bodies) much reduced in size and the stroma proliferated. The bronchial and cervical lymphatic glands were enlarged, but, with the exception of a small overgrowth of the stroma in the centre of the lymph nodes, histologically normal. The liver was normal. The kidneys were normal in substance, but the pelvis of each was surrounded by a soft mass of dark-red splenic-looking tissue which microscopically showed the structure of myeloid tissue. The erythroblasts in it were mostly megaloblastic; the eosinophil myelocytes were particularly abundant; there were many non-granular cells (? pre-myelocytes or 'myeloblasts'), which perhaps corresponded with the excess of hyaline cells in the blood; there were many plasma-cells; the connective tissue stroma was very slight. The true nature of the change was not suspected by the authors until they saw the specimens described by McKenzie, Browning, and Dunn, in the paper to which I have just referred.

The above are the only two English writings on the subject that I can find. At the meeting of the Société Anatomique of Paris on October 28, 1910, Léon Tixier (13) showed the kidneys of an infant, aged 10 months, who died from pseudoleukaemic anaemia. The hilus in both kidneys was occupied by a reddish mass, macroscopically resembling blood-clot. Microscopically this tissue was found to have the characters of red bone-marrow in a state of haemopoietic activity. It included erythroblasts, myelocytes, bone-marrow giant-cells (megakaryocytes), undifferentiated cells of 'lymphocyte' type, all of them bound by a scanty reticulum of connective tissue to blood-vessels of embryonic type.

In 1912 Takehiko Tanaka (14), a Japanese doctor working with W. H. Schultze, described two cases of 'anaemia pseudoleukaemica infantum' (infantile splenic anaemia) in which the post-mortem examination showed a development of bone-marrow tissue in the connective tissue of the kidney

hilus. The first case, which was also shortly described by Schultze (15), was that of a male child, with extremely severe rickets and the signs of infantile splenic anaemia, who died of broncho-pneumonia at the age of  $1\frac{3}{4}$  years. The blood-count, taken about six months before the child's death, gave haemoglobin, 60 per cent.; red cells 4,000,000, and white cells 8,000, per cubic millimetre of blood. Two months before death the child had epistaxis and purpura. The necropsy and microscopical examination showed that the bone-marrow was in a state of so-called 'lymphoid degeneration', with great excess of erythroblasts, myeloblasts, and lymphocytes. There was a certain amount of myeloid change in the spleen, liver, lymphatic glands, and the kidneys, but the most remarkable change was a development of bone-marrow tissue in the connective tissue of the hilus of both kidneys. The tissue in question macroscopically had the appearance of being infiltrated with effused blood (excellent illustrations of the macroscopic and microscopic appearances accompany the description of the case), but microscopically showed an infiltration with bone-marrow elements, especially myeloblasts, many of which were in process of karyokinesis. These myeloblasts were cells with large vesicular nuclei and clear basophilic cytoplasm free from neutrophil or eosinophil granules, and giving a positive 'oxydase reaction'. Accompanying the myeloblastic infiltration were erythroblasts, neutrophil and eosinophil myelocytes, lymphocytes, plentiful erythrocytes, and a few bone-marrow giant-cells (megakaryocytes).

The second case was that of a female child, aged 2 years, suffering from extremely severe rickets, infantile splenic anaemia, and pneumonia. The blood-serum gave a negative Wassermann reaction for syphilis. Death occurred about  $3\frac{1}{2}$  weeks after admission to the hospital. The necropsy and microscopical examination showed hardly any myeloid change in the spleen, liver, lymphatic glands, and the cortical and medullary tissue of the kidneys. The myeloid change was practically limited to the hilus of the kidneys, the connective tissue of which, as well as the mucous membrane of the renal pelvis, was infiltrated with bone-marrow elements, especially erythroblasts and cells resembling myeloblasts. These latter cells were, however, really of a type transitional between myeloblasts and myelocytes, inasmuch as their basophil cytoplasm was often found to contain neutrophil or eosinophil granules. A feature of the second case was the absence of any trace of haemorrhage in the mucous membrane of the renal pelvis or in the hilus (I understand), so that Tanaka thinks it unlikely that the bone-marrow cells constituting the cellular infiltrations in question were merely the result of proliferation of cells derived from the circulating blood-stream.

Of some interest in this connexion are the experiments of Sacerdotti and Frattin (1902) (16), who artificially induced the formation of true bone and bone-marrow tissue in the hilus of the kidneys of rabbits by ligaturing the renal blood-vessels. These experiments were afterwards confirmed by J. F. Poscharissky (1905) (17), and by A. Maximow (1907) (18).

It is perhaps just worth while mentioning that Gierke (19) described a case



in which a circumscribed mass of bone-marrow-like tissue was found embedded in the suprarenal gland, and O. Brian (20), in another case, described a tumour-like growth of myeloid tissue between the kidney and the suprarenal gland.

In my recent case (Case VI), in connexion with the child's acute myeloid (myeloblastic) leukaemia, it is clear that symmetrical leukaemic haemorrhages occurred, and were associated with symmetrical growths of myeloid tissue at the hilus of each kidney. Until more is known of the true nature and causation of leukaemia one cannot definitely assert that leukaemic growths of myeloid tissue, whether in the bone-marrow or in other (extramedullary) tissues and organs, can ever be regarded as having a conservative value, that is to say, as representing a vital reaction (on the part of the affected organism) of a (in the 'modern teleological' sense) conservative, supplementary nature. In connexion with the occurrence of symmetrical haemorrhages in myeloid leukaemia, I would refer to certain published cases of patients with myeloid leukaemia suddenly developing the symptoms of acute (apoplectiform) Ménière's disease (vertigo, &c.). In one such case, which with the help of Mr. Richard Lake I described in 1900, (symmetrical) leukaemic haemorrhage was found in both internal ears. The illustrated account of the case (21) contains references to various similar cases from the literature of the subject, and a few other cases of the same nature have been published since then (22).

## REFERENCES.

1. Ward, G. R., 'Nodular Leukaemia', *Proc. Roy. Soc. Med., Medical Section*, Lond., 1912, v. 73.
2. Sternberg, C., at the end of his paper 'Zur Kenntnis des Chloroms (Chloromyelom)', Ziegler's *Beiträge z. path. Anat. u. z. allg. Path.*, Jena, 1905, xxxvii. 437.
3. Cf. Weber, F. Parkes, and Wolf, F., 'Mediastinal Leukosarcomatosis', *Amer. Journ. Med. Sci.*, Philadelphia, 1916, clii. 231.
4. Naegeli, O., *Blutkrankheiten und Blutdiagnostik*, 2nd edit., Leipzig, 1912, 93.
5. Cf. Dunn, J. S., 'The Use of the Oxydase Reaction in the Differentiation of Acute Leukaemias', *Quarterly Journal of Medicine*, Oxford, 1913, vi. 293.
6. Mager, W., 'Zur Klinik der Leukosarkomatose', *Wiener Med. Wochenschrift*, 1909, lix, col. 1877.
7. O'Kelly, W. D., *Dublin Journal Med. Sci.*, 1914, cxxxvii. 409.
8. *St. Bartholomew's Hospital Reports*, London, xlii. 207 (Museum specimen No. 2309, b. 4).
9. Weber, F. Parkes, and Ledingham, J. C. G., 'Mediastinal Form of Lymphadenoma', *Proc. Roy. Soc. Med., Clinical Section*, Lond., 1909, ii. 66.
10. Cf. Weber, F. Parkes, 'Congenital Valvular Defects on the Left Side of the Heart', *St. Bartholomew's Hospital Reports*, London, 1899, xxxv. 147.
11. McKenzie, Ivy, Browning, C. H., and Dunn, J. S., 'The Occurrence of Bone-marrow in the Hilum of the Kidney in Children', *Journ. of Path. and Bact.*, Cambridge, 1909-10, xiv. 139.
12. Fawcett, J., and Boycott, A. E., 'Bone-marrow in the Hilum of the Kidney', *Journ. of Path. and Bact.*, Cambridge, 1909-10, xiv. 404.
13. Tixier, Léon, 'Myélome du rein dans un cas d'anémie pseudoleucémique', *Soc. Anatom. de Paris*, Séance du 28 oct. 1910.



14. Tanaka, T., 'Ueber Knochenmarkgewebsentwicklung im Nierenhilusbindegewebe bei Anaemia Splenica', *Ziegler's Beiträge z. path. Anat. u. z. allg. Path.*, Jena, 1912, liii. 338-52.
15. Schultze, W. H., 'Ueber tumorförmige Bildung myeloiden Gewebes im Bindegewebe des Nierenhilus', *Verhandl. d. Deut. Path. Gesellschaft*, 1912, Fünfzehnte Tagung, 45-7.
16. Sacerdotti, C., and Frattin, G., 'Ueber die heteroplastische Knochenbildung', *Virchow's Arch.*, Berlin, 1902, clxviii. 431-43.
17. Poscharissky, J. F., 'Ueber heteroplastische Knochenbildung: eine path.-hist. u. exp. Untersuchung', *Ziegler's Beitr. z. path. Anat. u. z. allg. Path.*, Jena, 1905, xxxviii. 135-76. There is an excellent plate confirming Sacerdotti's experiments.
18. Maximow, A., 'Experimentelle Untersuchungen zur postfötalen Histogenese des myeloiden Gewebes', *Ziegler's Beiträge z. path. Anat. u. z. allg. Path.*, Jena, 1907, xli. 122-66.
19. Gierke, 'Ueber Knochenmarksgewebe in der Nebenniere', *Ziegler's Beiträge z. path. Anat. u. z. allg. Path.*, Jena, 1905, suppl. vii. 311.
20. Brian, Otto, 'Ueber eine aus Knochenmark bestehende Geschwulst zwischen Niere und Nebenniere', *Virchow's Arch.*, Berlin, 1906, clxxxvi. 258-87.
21. Weber, F. Parkes, and Lake, R., 'Acute Ménière's Symptoms in Spleno-medullary Leucocythaemia', *Medico-Chirurgical Transactions*, London, 1900, lxxxiii. 185. Cf. F. W. Mott, *ibid.*, lxxxiii. 209.
22. Cf. Kock, A., *Zeitschrift für Ohrenheilkunde*, Wiesbaden, 1905, 1. 412.

#### ADDITIONAL NOTE.

Since writing this paper the account of a case of 'Thymus Tumor associated with Acute Lymphatic Leukaemia', by R. H. Major, has appeared in the *Bulletin of the Johns Hopkins Hospital*, Baltimore, 1918, xxix. 206. The patient was a white woman, aged 42 years. At the post-mortem examination a tumour, apparently derived from the thymus gland, was found in the anterior mediastinum, extending down over the heart. The posterior surface of the tumour was closely adherent to the parietal pericardium. By microscopical examination the tumour was seen to contain bodies resembling degenerated Hassall's corpuscles. Dr. Major refers to similar cases which have been described in the literature of the subject, and discusses Sternberg's suggestions in regard to the nature of so-called leucosarcomatosis.

DESCRIPTION OF ILLUSTRATIONS.

PLATE 13, FIG. 1. *Case VI.* Röntgen skiagram of the thorax from the front (May 13, 1918), showing the tumour-like growth in the superior mediastinum above the heart.

FIG. 2. *Case VI.* Diagrammatic drawing (made directly after the necropsy) of the heart, covered by the unopened pericardium, with the tumour-like mass at its base. The anterior surface of the latter has been cut away from the posterior surface of the sternum. The drawing shows the relative positions of the heart and growth, and may be compared with the Röntgen skiagram (Fig. 1) taken during life.

PLATE 14, FIG. 3. *Case VI.* Coloured drawing of the right kidney as it appeared, when cut open, soon after the necropsy. It shows the position of the red myeloid (and haemorrhagic) tissue at the hilus, filling up the space between the kidney substance and renal pelvis, normally occupied by connective tissue and fat. The kidney substance looked paler when the kidney was first cut into. The appearances in both kidneys were identical.

PLATE 15, FIG. 4. *Case VI.* Microscopical drawing of part of the tissue (stained with haematoxylin and eosin) from the hilus of the kidney, showing myeloblasts and uninuclear and multinuclear bone-marrow giant-cells (megakaryocytes). The erythrocytes were for some reason not stained, and are therefore not represented in the drawing. Magnification, 950.

PLATE 14, FIG. 5. *Case VI.* Microscopical coloured drawing (about the same magnification) from another piece of the tissue occupying the renal hilus. It shows three remaining fat vesicles, with erythrocytes (haemorrhage) and myeloblasts (or 'non-granular myelocytes'). The section was stained by Leishman's method.



CASE VI

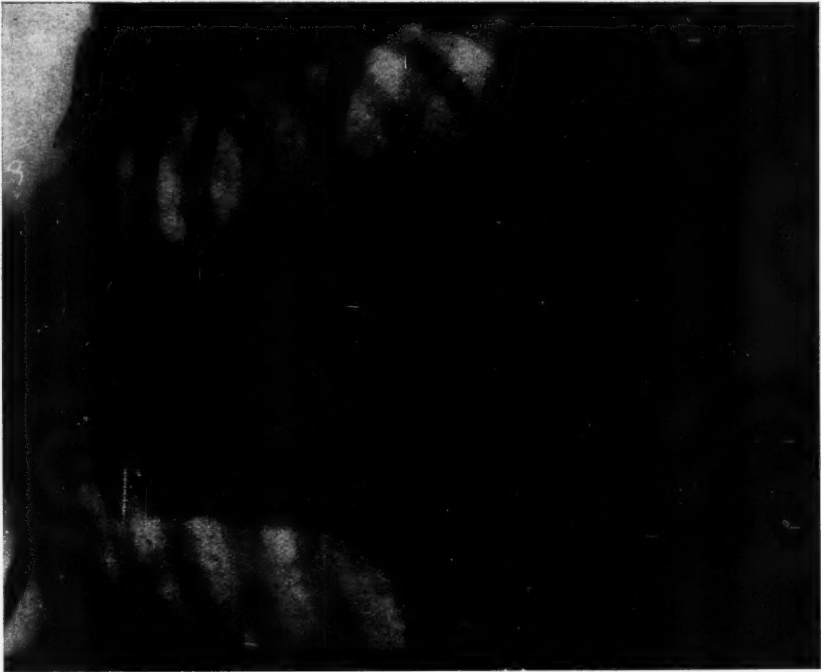


FIG. 1. Röntgen skiagram of the thorax from the front (May 13, 1918), showing tumour-like growth.

CASE VI

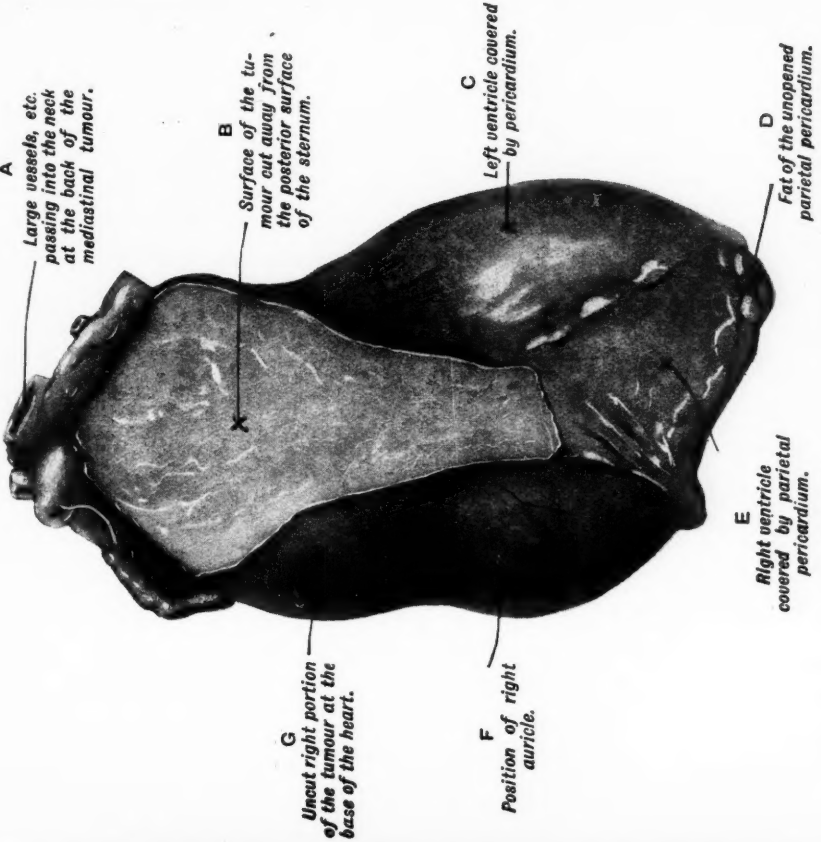


FIG. 2. Diagrammatic drawing to show relative position of the heart and the large tumour at the base of the heart.



CASE VI.



FIG. 3. Coloured drawing of the right kidney.



FIG. 5. Microscopic drawing, showing fat vesicles, erythrocytes, and myeloblasts.





CASE VI

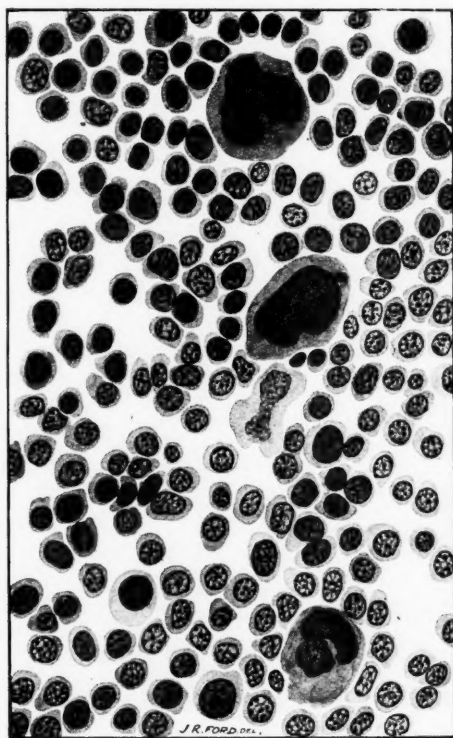


FIG. 4. Microscopic drawing of part of the tissue from the hilus of the kidney, showing myeloblasts and bone-marrow giant-cells.



# OBSERVATIONS UPON TWO CASES OF DIABETES INSIPIDUS: WITH AN ACCOUNT OF THE LITERATURE RELATING TO AN ASSOCIATION BETWEEN THE PITUITARY GLAND AND THIS DISEASE

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## I. DESCRIPTION OF TWO CASES.

*Case I.* Charles L., aged 22, admitted 2.9.15 under care of Dr. W. Essex Wynter.

*History.* About the end of June 1915 patient received accidentally a stab with a bayonet in lower part of the left orbit. He states that the wound healed in a week, while the eye remained bloodshot for a fortnight. He noticed considerable thirst on evening of day of accident, and is quite certain that the thirst and polyuria date from this day. Since the accident he has been completely blind in left eye.

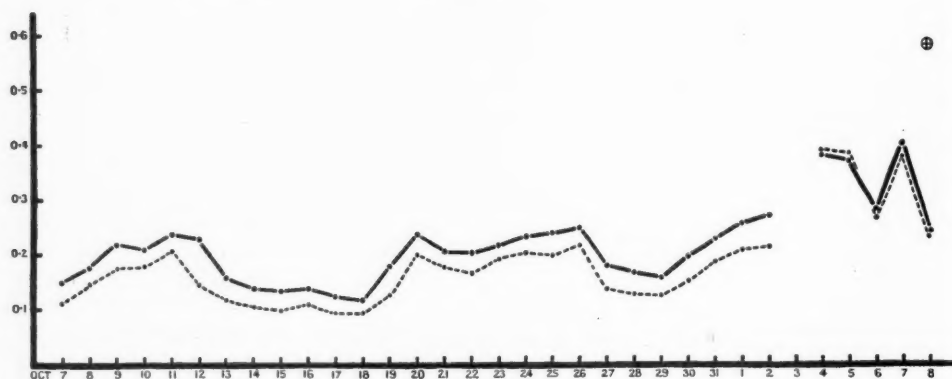
*State on admission.* Patient complained of weakness, loss of flesh, thirst, and polyuria. Wassermann reaction negative. The patient's eyes were examined by Mr. Affleck Greeves, who reported that the right fundus was normal, and the left disk completely atrophic; there was no perception of light in the left eye. Skiagram of the head showed 'abnormal smallness of the pituitary fossa'.

During the first four weeks after admission the volume of urine increased from about 3 litres to 7 or 8 litres daily (Table I). Administration of a pituitary preparation by the mouth (September 13 to 18) caused no improvement.

TABLE I. *Case I.*

Day's volume of urine in c.c.

Sept. 3	2840	Sept. 13	5680		Sept. 23	7100
4	3120	14	5400	Two pituitary tablets daily	24	6810
5	3960	15	8060		25	7040
6	4090	16	6360		26	7100
7	5110	17	6250		27	8100
8	4830	18	7100		28	7380
9	5400	19	6980			
10	5680	20	6810			
11	5560	21	6640			
12	5280	22	6810			

FIG. 1. *Case I.*Continuous line represents  $\Delta$  of urine.⊙ represents  $\Delta$  of serum.

Dotted line represents nitrogen + chlorine of urine in grm. per cent.

Subsequently (from September 29 onwards) daily analyses of the urine were made (Table II). The maximum volume recorded was 8,610 c.c. in the twenty-four hours. The specific gravity during the first month was never above 1,004, and was on many occasions not perceptibly above 1,000 as measured by the ordinary specific gravity bulb. The depression of freezing-point ( $\Delta$ ) is shown in Fig. 1. The lowest figure obtained was  $0.114^{\circ}$ ,<sup>1</sup> whereas the  $\Delta$  of the patient's serum ( $0.572^{\circ}$ ) was at the upper limit of the normal range ( $0.55$  to  $0.57^{\circ}$ ). The difference in osmotic pressure of these two fluids is approximately as follows (the correction for body temperature is neglected since it affects both fluids):

	$\Delta$	Osmotic pressure mm. Hg.
Serum	$0.572^{\circ}$	5080
Urine	$0.114^{\circ}$	1000
Difference		4080

<sup>1</sup> The smallest  $\Delta$  of urine recorded appears to be  $0.075^{\circ}$  (Macallum and Benson, 71). This result was obtained in a normal person after drinking water (amount not stated); 205 c.c. urine were secreted in ten minutes, which is at the rate of nearly 30 litres per day. Normal urines of specific gravity from 1,010 to 1,030 would show a  $\Delta$  of from  $0.6^{\circ}$  to  $2.0^{\circ}$  (see Meyer (72), p. 37).

This difference of pressure ( $5\frac{1}{2}$  atmospheres) gives, of course, no expression of the total work done by the kidney (see Cushny (64), p. 32). The maximum  $\Delta$  observed in the series of thirty-two measurements was  $0.402^\circ$  on November 7, when the patient was recovering; this is still considerably below that of the serum.

As a check upon the accuracy of the determinations of  $\Delta$ , the figures representing the sum of the nitrogen and chlorine of the urine have also been plotted in Fig. 1; this quantity must be proportional to a very large fraction of the total solids of urine, since the sulphates and in part the phosphates, as products of protein metabolism, will vary in the same manner as the nitrogen. It will be seen that there is very close parallelism between the two sets of figures.

The lowest concentrations of chlorine observed were 0.0199 per cent. on October 30 and November 8; it is remarkable that these minima occurred when the polyuria had diminished considerably. Three determinations of chlorine in the patient's serum gave 0.358 per cent., 0.359 per cent., and 0.360 per cent. by volume respectively; Schmidt's (73) analyses, when recalculated by volume, would give 0.363 per cent. as a normal figure. The chlorine on the days in question was then eighteen times more dilute in the urine than in the plasma, whereas in a urine of the type regarded as normal it is about  $1\frac{1}{2}$  times more concentrated (Table VIII). The urea nitrogen was estimated upon several occasions and was found to constitute a normal percentage of the total nitrogen (83 to 89 per cent.). The lowest percentage of total nitrogen found in the urine was 0.060 per cent. on October 17; supposing urea to have made up 85 per cent. of this, and the amount of urea in the blood to have been normal (13 mg. urea nitrogen per cent.), the urea was only four times more concentrated in the urine than in the blood, whereas a sixty- to eighty-fold concentration is effected under normal conditions.

From October 6 the intake of protein and salt was diminished in the hope that the excretion of smaller amounts of urea and chloride would lessen the diuresis. From October 13 onwards the diet was still more strictly regulated; it consisted of rusks, porridge, rice, suet pudding, butter, sugar, carrots, onions, and celery. Meat, milk, and salt were excluded, as also potatoes on account of unpalatability without salt, and bread on account of the amount of salt which is added by the baker. By these measures, the day's output of nitrogen and of chlorine, which was already low, was reduced to about one-half, and after some days the volume of urine fell from about 8 to about 6 litres. As the daily excretion of nitrogen now stood at only 4 grm., so that no further reduction could be expected, and that of chlorine at 2 grm., or about one-fifth the output of a person on ordinary diet, it is evident that no great success attended this form of treatment. From this time onward it became evident that the patient was recovering; the volume of urine fell to from 2 to 3 litres daily, and  $\Delta$  rose from  $0.15^\circ$  to  $0.4^\circ$  (November 8); this latter is still a low figure, and the specific gravity did not rise above 1.006. The low absolute amounts of nitrogen and



TABLE II. Case I.

The maximum and minimum figures are indicated by italics.

Date.	Volume c.c.	Specific gravity.	Δ.	Chlorine.		Nitrogen.		Chlorine + Nitrogen.		Urea. mg. %.	Urea Nitrogen. % of total nitrogen.	Diet.
				mg. %.	grm. per day.	mg. %.	grm. per day.	mg. %.	grm. per day.			
Sept. 29-30	8670	1001		34.80	2.99	96.60	8.31	131.40	11.30	179	86.9	Ordinary
30-1	7540	1002		71.00	5.25	98.50	7.42	169.50	12.67	188	89.3	"
Oct. 1-2	6420	1001		25.50	1.64	92.40	5.93	117.90	7.57	178	89.8	"
Serum, Oct. 1				360								"
3-4	6890	1002		34.08	2.35	113.10	7.78	147.18	10.13	214	87.6	"
4-5	6080	1002		38.38	2.33	121.90	7.41	160.28	9.74	220	83.6	"
5-6	7390	1003		38.30	2.33	124.60	9.21	162.90	12.04			"
6-7	8000	1002		35.50	2.84	103.30	8.26	138.80	11.10			"
7-8	8225	1000.5	0.147	28.40	2.33	82.20	6.78	110.60	9.11			Restricted
8-9	8250	1002	0.175	45.40	3.71	100.00	8.25	145.40	11.96			"
9-10	7950	1002	0.218	53.97	4.29	119.80	9.46	173.27	13.75			"
10-11	7805	1003	0.208	53.22	4.54	119.80	9.34	178.02	13.88			"
11-12	6780	1001	0.233	71.00	4.81	134.80	9.14	205.00	13.95			"
12-13	8060	1002	0.224	32.66	2.61	108.90	8.77	141.50	11.38			"
13-14	8100	1002	0.153	24.14	1.95	91.50	7.41	115.60	9.96			Special
14-15	7620	1001	0.138	24.84	1.89	77.40	5.89	102.20	7.78			"
15-16	7000	1000	0.131	26.98	1.88	67.76	4.74	94.70	6.62			"
16-17	8150	1000.5	0.134	42.60	3.47	64.40	5.24	107.00	8.71			"
17-18	6850	1000.5	0.1205	29.82	1.98	60.00	4.11	89.80	6.09			"

TABLE II (continued).

Date.	Volume c.c.	Specific gravity.	Δ.	Chlorine.		Nitrogen.		Chlorine + Nitrogen.		Urea. mg. %.	Urea Nitrogen. % of total nitrogen.	Diet.
				mg. %.	gm. per day.	mg. %.	gm. per day.	mg. %.	gm. per day.			
Oct.												
18-19	6150	1000	0.1145	28.40	1.72	61.32	3.77	89.70	5.49			Special
19-20	5950	1000.5	0.1740	49.70	2.95	73.36	4.37	123.00	7.32			"
20-21	3150	1004	0.2350	42.6	1.35	156.80	4.93	199.40	6.28			"
21-22	3180	1004	0.203	25.50	0.803	151.20	4.80	176.70	5.603			"
22-23	5900	1002	0.200	35.50	2.094	129.00	7.61	164.50	9.704			Ordinary
23-24	5460	1002	0.213	42.60	2.32	147.30	8.04	189.90	10.36			"
24-25	6500	1002	0.2305	53.96	3.51	147.00	9.58	200.90	13.09			"
25-26	5780	1003	0.236	53.96	3.12	142.80	8.26	196.70	11.38			Special
26-27	4930	1002	0.247	73.80	3.63	140.70	6.93	214.50	10.56			"
27-28	5520	1002	0.178	25.50	1.407	109.20	6.02	134.70	7.427			"
28-29	5620	1002	0.164	22.70	1.27	105.00	5.90	127.70	7.17			"
29-30	5750	1002	0.157	29.80	1.725	94.20	5.41	124.00	7.135			"
30-31	3300	1003	0.193	19.98	0.66	129.50	4.27	149.50	4.93			"
31-1	2480	1003	0.228	38.30	0.94	150.00	3.72	188.30	4.66			"
Nov.												
1-2	3450	1005	0.253	53.96	1.86	154.70	5.33	208.60	7.19			"
2-3	2600	1003	0.270	72.40	1.88	138.00	3.58	210.40	5.46			Ordinary
4-5	1950	1006	0.382	72.40	1.41	314.00	6.12	386.40	7.53			"
5-6	3210	1005	0.369	66.00	2.12	319.00	10.24	385.00	12.36			"
6-7	2700	1004	0.279	36.90	0.99	230.00	6.21	266.90	7.20			"
7-8	2100	1003	0.402	41.20	0.86	339.50	7.13	380.60	7.99			"
8-9	4900	1002	0.240	19.68	0.97	213.00	10.43	233.00	11.40			"
Serum,												
Nov. 8			0.572	{								
				358								
				359								

chlorine show that this persistently dilute character of the urine was due in part to the small amount of food taken, although the patient was on unrestricted diet.

The patient was then discharged at his own request; we have been unable to learn his subsequent history.

It is possible that the wound in the orbit in this case caused some disturbance in the region of the pituitary, perhaps by haemorrhage and thrombosis extending along the cavernous sinus; the immediate onset of thirst and polyuria is very reminiscent of Cushing's account (23) of the effect in dogs of removal of the posterior lobe of the pituitary or division of its stalk. Probably some further complication occurred in our patient, since when he first came under observation two months after the injury the polyuria was of only moderate degree (3 litres daily). Thereafter the volume of urine showed a well-marked wax and wane, which may be summarized roughly as follows:

*Day's Volume of Urine.*

Increase from 3 to 8 litres during four weeks. Table I.

Maintenance at 6 to 8 litres during two weeks } Table II.

Decrease from 8 to 2 litres during three weeks }

One must suppose that the recovery in the last period was due to resolution of the products of the lesion.

*Case II.* Isabel S., aged 54, admitted 3.1.17 under care of Mr. T. H. Kellock.

*History.* Lump first noticed in left breast ten years before. This increased in size very slowly, and breast was amputated two years before at York County Hospital. Microscopic examination showed growth to be a carcinoma. About fifteen months after operation fresh nodules appeared in right breast, in neck, and under arms.

*State on admission.* Patient complained of loss of flesh, weakness, and great thirst. The volume of urine was from 7 to 8 litres daily. Wassermann reaction negative. No recurrence at site of operation. Subcutaneous nodules of growth in right breast, right axilla, right and left supraclavicular fossae and mid-sternomastoid lymph glands, and around umbilicus. Examination of nervous system by Dr. Campbell Thomson showed no signs of organic disease. Tendon reflexes in arms and legs brisk; both plantar reflexes flexor. The visual fields were examined by Mr. Arnold Lawson, who reported that there was no indication of pituitary involvement in ocular condition except possible association with central amblyopia in both eyes. Skiagram of the head taken by Dr. Kingsbury showed a shadow 1 inch in length and  $\frac{1}{2}$  inch in depth situated about  $\frac{1}{2}$  inch above the sella turcica. The anterior end of the shadow was above the posterior clinoid process and the shadow appears to run almost directly backwards.

The case was regarded as probably one of metastasis of carcinoma in the pituitary similar to those recorded by Simmonds and Sekiguchi (see under III

TABLE III. Case II.

*Effect of Diet and of Pituitrin by Mouth.*

	Jan.	Volume c.c.	Specific gravity.	Chlorine.		Nitrogen.		Chlorine + Nitrogen.		
				mg. %.	grm. per day.	mg. %.	grm. per day.	mg. %.	grm. per day.	
Period 1	7-8	8980	1002 1003	26.2 106.0	9.46	141	12.59	247	22.05	Δ on Jan. 7. } Ordinary Serum, 0.575° } diet Urine, 0.29° }
Period 2	8-9 9-10 10-11 11-12 12-13 13-14 14-15 15-16 16-17 17-18	6650 4850 5000 5200 6000 7590 7760 5300 5440 7000	1004 1004 1003 1003 1004 1003 1004 1005 1003 1002	69.6 29.8 35.5 27.0 24.1 56.8 62.4 56.8 48.3 34.1	4.63 1.44 1.77 1.40 1.45 4.31 4.84 3.01 2.63 2.38	176 184 179 157 133 109 116 161 153 140	11.70 8.92 8.95 8.16 7.98 8.27 9.0 8.58 8.34 9.80	246 214 214 184 157 166 178 201 174	16.33 10.36 10.72 9.56 9.43 12.58 13.84 11.54 10.97 12.18	Special diet
Mean of Period 2		6079		44.4	2.78	150.8	8.96	195.2	11.75	
Period 3	22-23 23-24 24-25 25-26 26-27 28-29 29-30	4830 5100 6430 5800 6460 6360 5810	1006 1005 1005 1005 1004	63.2 76.0 96.0 78.8 82.4 98.7 91.0	3.05 3.87 6.17 4.57 5.32 6.30 5.30	209 183 174 161 147 164 176	10.10 9.35 11.20 9.30 9.50 10.50 10.25	272 259 267 240 229 263 267	13.1 13.2 13.3 13.9 14.8 16.7 15.5	Ordinary diet 1 c.c. pituitrin by mouth daily
Mean of Period 3		5827		83.7	4.94	173.4	10.03	256.7	14.9	

TABLE IV. Case II.  
*Effect of Pituitrin sub cutem.*

Period 4	Volume c.c. per hour.	Chlorine.		Nitrogen.		Chlorine + Nitrogen.		<i>Pituitrin sub cutem</i> 1 c.c. at 2 p.m. 30th
		mg. %.	gm. per day.	mg. %.	gm. per day.	mg. %.	gm. per day.	
Jan. 30-31	2900	123.5	3.58	311	9.02	434	12.6	
Feb. 1-2	3380	160	5.47	316	10.8	476	16.3	
2-3	4290	123	5.27	253	10.85	376	16.1	0.5 c.c. at 2 p.m. 1st
4-5	6380	65	4.16	157.	10.05	222	14.2	0.5 c.c. at 2 p.m. 2nd
5-6	3200	92.3	2.95	311	9.95	403	12.9	none
6-7	6900	59.6	4.11	168	11.59	228	15.7	1 c.c. at 2.30 p.m. 5th
7-8	137	287		660		947		none
from 4 to 6 p.m. 7th	6320	105		175		280		1 c.c. at 2.30 p.m. 7th
rest of 24 hours	6457	109	7.02	185	11.96	294	18.98	
whole 24 hours	7640	83	6.34	147	11.23	230	17.57	none
8-9								
9-10	305	284		481		765		
2.30 p.m. to 5.50 p.m. 9th	127	1014		728		969		
from 5.50 to 7.45 p.m. 9th	3720	118		224		342		
rest of 24 hours	4152	134	5.56	258	10.71	392	16.27	
whole 24 hours	7600	71	5.39	142	10.8	213	16.19	none
11-12								
12-13	235							
2.30 p.m. to 5.15 p.m. 12th	110	209		528		737		1 c.c. at 2.30 p.m. 12th
from 5.15 to 7.15 p.m. 12th	420							
from 7.15 to 11 p.m. 12th	3640	89.5		161		250		
rest of 24 hours	4405	111	4.88	225	9.90	336	14.78	
whole 24 hours								
Average of 7 days when pituitrin given	4112	122	4.96	266	10.31	388	15.27	
Average of 4 days when no pituitrin given	7130	69.6	5.00	153	10.92	223	15.92	

below). The urine was somewhat less dilute than in Case I; the specific gravity was never observed to be below 1,002. The  $\Delta$  of the urine measured on two occasions was 0.29° and 0.375°, that of the serum being 0.575°. The lowest concentrations of chlorine (0.024 per cent.) and of total nitrogen (0.109 per cent.) were higher than in Case I (see Table VIII). Two analyses of the chlorine of the serum gave 0.381 per cent., a somewhat high figure, but these were carried out upon 1 c.c. only by the ordinary method. The urea nitrogen constituted a normal percentage of the total nitrogen (79 to 81 per cent.).

*Treatment. (1) By Diet.*

The patient was at first placed upon a diet poor in protein and without added salt, similar to that used for Case I. The nitrogen and chlorine of the urine were by this means reduced to about one-half (Table III), and the volume of urine fell from nearly 9 to 5 litres. The effect, however, was transient and the volume of urine soon rose again to 7 litres.

*(2) By Pituitary Extract.*

The patient was then given 1 c.c. pituitirin by mouth twice daily for eight days (Table III); this had no appreciable effect upon the polyuria (see under II *b*, below), the average day's volume being 6,079 c.c. before, and 5,827 c.c. during this treatment. However, when the extract was given *sub cutem* (Table IV), a very different result was obtained; the effect was quite apparent even in the whole twenty-four hours' urine (January 30 to February 7), the volume being reduced by the single injection to about one-half, and the specific gravity raised from 1,003.4 to 1,006.7. Subsequently (February 8 to 13) the urine was collected over short intervals after the injection; during the first two hours a practically normal urine of specific gravity 1,014-16 was secreted, the hourly volume-rate being about one-quarter of that for the whole day. The effect was still very noticeable up to the ninth hour after the injection (February 13). These observations are summarized in the averages given at the end of Table IV.

*Averages.*

	Volume c.c. per day.	Chlorine + Nitrogen mg. %.	gram. per day.
Pituitirin <i>sub cutem</i>	4112	388	15.27
No pituitirin	7030	223	15.92

The injection was always followed by an action of the bowels, but no ill effects of any kind were observed.

In order to investigate further this remarkable anti-diuretic action of pituitary extract, control observations were made upon a person showing no abnormality of the urine (Table V). An effect of exactly the same type was



TABLE V.  
*Control Observations upon Effect of Pituitirin sub cutem.*

16th to 17th.				17th to 18th.				18th to 19th. 1 c.c. pituitirin sub cutem at 2 p.m. on 18th.			
Time.		Urine.		Time.		Urine.		Time.		Urine.	
		c.c.	c.c. per hour.			c.c.	c.c. per hour.			c.c.	c.c. per hour.
2 p.m.		114	65	2 p.m.		170	75	2 p.m.		85	28
3.45 p.m.				4.15 p.m.		57	76	5 p.m.			1021
7.45 p.m.		341	85	5 p.m.		142	57	10 p.m.		142	28
				7.30 p.m.				5.30 a.m.		294	38
5.30 a.m.		341	35	5.30 a.m.		540	54	2 p.m. to 5.30 a.m.		Total 511	Mean 33
2 p.m. to 5.30 a.m.		Total 796	Mean 51	2 p.m. to 5.30 a.m.		Total 909	Mean 60	5.30 a.m. to 2 p.m.		Total 880	Mean 103
5.30 a.m. to 2 p.m.		Total 965	Mean 114	5.30 a.m. to 2 p.m.		Total 1108	Mean 130	Whole 24 hours		1391	58
Whole 24 hours		1761	73	Whole 24 hours		2017	84				

TABLE VI. Case II.

*Salt Diuresis.*

	March	Volume c.c.	Specific gravity.	Chlorine.		Nitrogen.		Chlorine + Nitrogen.		Special diet as in Period 2 + 3 gm. NaCl daily
				mg. %.	gm. per day.	mg. %.	gm. per day.	mg. %.	gm. per day.	
Period 5	1-2	6300	1004	55.4	3.49	132	11.46	237	14.95	12 gm. NaCl on 6th " " 7th " " 8th " " 9th 12 gm. NaCl = 7.28 gm. Cl
	2-3	6410	1004	49.7	3.18	147	9.33	197	12.51	
	4-5	6700	1004	58.2	3.90	143.5	9.61	202	13.5	
	5-6	7000	1004	65.3	4.57	140	9.80	205	14.37	
Period 6	6-7	7430	1004	71.6	5.35	132	9.87	204	15.2	
	7-8	10560	1004	106.5	11.24	116	12.25	222	23.5	
	8-9	9280	1002	118	10.94	114	10.6	232	21.54	
	9-10	9400	1003	121	11.37	106	9.96	227	21.3	
	10-11	8230	1004	104.3	8.58	110	9.04	214	17.6	
	11-12	7700	1004	85.2	6.56	117.6	9.05	203	15.6	
	12-13	6810	1003	72.4	4.93	157.5	10.72	230	15.65	
	13-14	6580	1003	45.4	2.99					
Average of Period 5		6600		57.2	3.73	153	10.05	210	13.83	
Average of Period 6		8494		97.0	8.42	122	10.21	219	13.63	

observed. The specific gravity was raised from 1,010 to 1,020; the hourly volume-rate during the twelve hours following the injection was reduced to nearly one-half, and this diminution is still distinctly perceptible in the whole twenty-four hours' volume. Pituitary extract has then a very distinct anti-diuretic action both in the normal body and in cases of diabetes insipidus.

*Observations on the Capacity of the Kidney for Concentration.*

An attempt was made to estimate the power of the kidney to secrete a more concentrated urine. After a preliminary period of four days the patient received 12 grm. sodium chloride daily for four days, a further period of three days being allowed for the complete excretion of the salt. The results are shown in Table VI. The volume of urine was increased from about 6.5 to 8.5 litres, but the kidney was nevertheless excreting chloride at nearly double the previous concentration, the average percentage of chlorine being in the preliminary period 57 mg., and during the diuresis 97 mg. It is then evident that, as far as the excretion of chloride is concerned, the kidney was capable of producing a concentration greater than that reached under ordinary circumstances. But the additional 2 litres of water excreted with the salt of course served to dilute the other constituents of the urine, and it would seem that a remarkably exact compensation was brought about in this way, for the average percentage of nitrogen+chlorine is almost the same in the two periods (210 mg. before and 219 mg. during the diuresis). The  $\Delta$  of the urine was not measured, but since there is a very close parallelism between  $\Delta$  and the concentration of nitrogen+chlorine (Fig. 1) it is highly probable that the kidney produced a fluid of the same molecular concentration during both periods.<sup>2</sup>

This adjustment is shown by Meyer's (72) cases, in which  $\Delta$  was measured; the ingestion of 20 grm. NaCl did not alter the molecular concentration of the urine. As controls, he gives the results of administration of salt to two patients convalescent from other conditions. The following table (Table VII) is compiled from Meyer's figures.

Apparently the convalescents were not on a constant diet, which may account for some irregularity in the figures, but the estimations of  $\Delta$  show quite distinctly the difference in the kidney's power of concentration in the normal body and in cases of diabetes insipidus. Meyer employed this test as a means of diagnosis between diabetes insipidus and primary polydipsia.<sup>3</sup> Rosenfeld (8) showed further that the capacity of the kidney in diabetes insipidus to concentrate salt was increased by about 50 per cent. when pituitary extract was given *sub cutem* (see p. 233).

<sup>2</sup> The data as to the work done by the kidney in these cases will be considered in a later communication.

<sup>3</sup> One may point out that Meyer is sometimes misquoted as maintaining that the concentration of *chloride* remains constant when salt is given in diabetes insipidus. He does not make any such statement, and in the light of his own figures could not well do so.

TABLE VII.

*Salt Diuresis. Meyer.*

		Volume c.c.	$\Delta$ .	NaCl mg. %.	NaCl + Nitro- gen mg. %.
<i>Diabetes insipidus</i>					
Case I	Day 1	8830	0.20	96	220
	2	7100	0.18	91	194
20 grm. NaCl taken	3	11512	0.18	148	220
	4	6600	0.17	115	211
Case II	1	5660	0.34	176	378
	2	6300	0.34	160	328
20 grm. NaCl taken	3	7560	0.34	290	388
	4	8220	0.31	199	298
<i>Convalescents</i>					
I	1	1740	1.10	726	1552
	2	1380	1.10	929	1877
20 grm. NaCl taken	3	1780	1.37	1124	1932
	4	3340	1.11	854	1378
II	1	1340	1.44	819	1917
	2	1300	1.48	995	2037
20 grm. NaCl taken	3	2140	2.32	1810	2722
	4	2310	1.01	795	1621

The additional salt given in these observations on our Case II (Table VI) was recovered quantitatively :

	Grm. Chlorine
Mean of two preceding days	4.23
Total in 7 days, Mar. 6-13	58.97
Subtract $4.23 \times 7$	29.61
Extra chlorine excreted	29.36
Chlorine given in 48 grm. NaCl.	29.13

(Such very close agreement is of course accidental, being dependent upon the days taken in calculating the previous mean output.)

The patient left the hospital in April 1917. In August 1918 we learned from her that she was suffering acutely from pains in the head, with dizziness, had very defective vision, and apparently double facial paralysis; the day's volume of urine was stated to be 2 gallons (9 litres).

The abnormal dilution of the urine in these two cases is best shown by a table similar to that given by Cushny (64) to illustrate the normal activity of the kidney.

TABLE VIII.

	mg. %.					Change in concentration effected by Kidney.		
	Plasma.	Urine.						
		'Normal.'	Minima.					
			Case I.	Case II.				
Urea	30	2000	110	186	'Normal.'	Case I.	Case II.	
Chlorine	360	600	20	24	$\times 60$ $\times 1.7$	$\times 4$ $\div 18$	$\times 6$ $\div 15$	

As one would expect, neither the chloride content nor  $\Delta$  of the serum give in either of these cases any evidence of altered concentration of the blood; this

alteration must be at any one moment extremely small. Case I weighed only 44 kilos; his blood-volume would have been therefore about 2 litres. The maximum day's volume of urine was nearly 9 litres, which is equivalent to 6 c.c. per minute. The addition to the blood at one moment of all the water passed through it in a minute would therefore dilute it by only 0.3 per cent.

## II. THE EFFECT OF PITUITARY EXTRACT UPON THE EXCRETION OF URINE.

### (a) *In the Normal Organism.*

The development of our knowledge of this subject has followed a rather curious course. The first observations were made in 1901 by Magnus and Schäfer (1) in experiments of comparatively short duration (half an hour) on animals; they found a diuretic effect which, in later experiments (Schäfer and Herring (2)), was not always obtained. Subsequent workers were by no means unanimous; Motzfeldt (3) gives a summary of the contradictory results of sixteen investigations by laboratory methods, in some of which a diuretic, in others an anti-diuretic, effect was observed.

However, from 1913 onwards several cases of diabetes insipidus were recorded (see under (b) below) in which the polyuria was lessened by pituitary extracts; these results caused renewed investigation to be made by more suitable methods of the effect in the normal body. It seems to be now established by the work of several observers, especially Korschegg and Schuster (5), Motzfeldt (3, 4), and quite recently (1918) Rees (6), that this action is chiefly anti-diuretic; and our control observations (Table V), which were made in ignorance of the published results of others, show an unmistakable anti-diuretic effect.

Korschegg and Schuster (5) injected pituitary preparations intravenously in rabbits; an average taken from all their experiments shows that the two-hourly volume of urine was in the controls 62 c.c., and after the injections 22 c.c. The first effect of the injection of a moderate dose is an increased flow of urine lasting from ten to twenty minutes; with larger doses this stage of diuresis does not occur. This transient diuretic action was observed also by Motzfeldt, but was found by him to occur in anaesthetized animals only. Probably this difference between the initial and subsequent effects is responsible for the contradictory results obtained by previous workers; the immediate increase would be very conspicuous in drop-recorder experiments of short duration. The water content of the blood was found to be raised from 84 per cent. to 86 per cent. during the period of diminished secretion. Korschegg and Schuster examined also the effect of subcutaneous injection of pituitary preparations in normal men; the day's volume of urine was reduced to nearly one-half. Results confirmatory of these were obtained in men by von der Velden (70); no constant alteration in the blood-pressure was found.

Motzfeldt (4) examined the two-hourly secretion of urine before and after

subcutaneous injection of pituitary extracts (three commercial products) in six patients and convalescents showing no polyuria; an average taken from all his figures (ten experiments) gives the following result:

	Urine, c.c. per hour.
During 4 hours before injection	140
During 4 hours after injection	66

The blood-pressure was in most cases lowered after the injection. The effect of administration by the mouth was not investigated. Two similar experiments with a preparation of the anterior lobe of the pituitary showed some increase in the flow of urine.

Motzfeldt (3) also carried out experiments upon rabbits which showed that both the normal flow of urine and the polyuria induced by introduction of water into the stomach were diminished for several hours by subcutaneous injection of pituitirin. He also obtained some anti-diuretic effect, apparently less distinct, by oral administration (cf. the results given under (b) below), but full protocols of the results are not given. Rees (6) experimented in a similar manner upon cats and rabbits, but extended his observations over periods of twenty-four hours. He found single injections to have no effect upon the day's volume of urine, the period of diminution being compensated for by a subsequent increase. The normal diuresis after administration of water by the stomach-tube reached its maximum in the second or third hour, and lasted about seven hours, while after simultaneous injection of pituitary extract it did not begin until the seventh hour, and then continued for about twelve hours, the total volume in the whole twenty-four hours being practically the same in the two cases. The work of Motzfeldt and Rees is discussed further under 'Discussion of Results' below.

The anti-diuretic action of pituitary extract appears to be shown further by the diminution in the ratio  $\frac{\text{urea in one hour's urine}}{\text{urea in 100 c.c. blood}}$  which occurs after subcutaneous injection of pituitirin (80), but the changes in the urea content of the blood in these experiments are somewhat irregular.

(b) *In Cases of Diabetes Insipidus.*

In Hoppe-Seyler's case (7) the patient showed adiposity and decrease of sexual power, but no signs pointing definitely to any affection of the pituitary. The results are presented in such a form as to give the maximum of trouble to the reader, but the following conclusion can be extracted from them:

	Average volume of Urine c.c. per day.
On 28 days when pituitirin was given <i>sub cutem</i>	2507
On 29 days when patient received no, or other, medicinal treatment (atropin, thyroid extract, or pituitirin, by mouth)	5630



Konschegg and Schuster (5) found the day's volume of urine to be reduced from 9 to 3.3 litres by subcutaneous injection of pituitirin; the  $\Delta$  of the urine, which was at other times about  $0.2^\circ$ , was raised to  $0.59^\circ$ , which is higher than that of normal serum. Rosenfeld (8) showed that sodium chloride (5 to 7 gr.) added to the food was excreted after subcutaneous injection of pituglandol in a concentration about 50 per cent. greater than that reached when no such injection was given. The anti-diuretic effect of pituitary extracts has been shown in other cases of diabetes insipidus by von der Velden (70), Farini (9), Kleeblatt (10), Graul (11), Orlandi (12), Erdheim (13), Römer (14), and Miller (15). In Römer's patient there was a tumour at the base of the brain invading the stalk and posterior lobe of the pituitary; this is the only case we have found recorded in which the effect of pituitary extracts has been tested upon a case shown subsequently to have a lesion of the gland.

Motzfeldt (3), while confirming in three cases of diabetes insipidus the anti-diuretic effect of subcutaneous injections of pituitirin and pituglandol, added the observation that similar benefit could be obtained by giving the fresh glands (ox) by the mouth; in one case seven whole glands, in another four posterior lobes, were taken every evening, whereby uninterrupted sleep was secured. Unfortunately he gives no figures showing the diminution in diuresis under this latter treatment. The anterior lobe, whether given in the fresh state by the mouth, or as extract subcutaneously, did not affect the quantity of urine; this confirms the earlier observations of Schäfer and Herring (2).

We obtained similar results by subcutaneous injection of posterior lobe extract (pituitirin) in our Case II, and showed the inefficacy of administration by the mouth in Cases I and II. These observations upon the anti-diuretic effect have since been confirmed by Barker and Mosenthal (16), Barker and Hodge (17), Rosenbloom (18), Williams (19), and Grundmann (20).

In none of the cases in which commercial preparations have been given by the mouth (Hoppe-Seyler, our Cases I and II, Miller, Rosenbloom, Williams) has any diminution in the volume of urine been observed, with the exception that von der Velden obtained some effect by administration of pituglandol in this way. Since the fresh gland is effectual when given by the mouth (Motzfeldt) it would seem that in the process of preparation the active principle becomes inabsorbable or liable to destruction in the alimentary canal. It would be well if Motzfeldt's method could be tried in other cases.

The following facts are brought out by the observations given in this section:

1. The subcutaneous injection of pituitary extract causes a diminished flow of urine for several hours; later this is compensated by an increased flow, so that the twenty-four hours' output may be unaltered.
2. The injection of a moderate amount sometimes causes an immediate decrease lasting for from ten to twenty minutes.

3. In cases of diabetes insipidus the injection of pituitary extract causes anti-diuresis as in the normal body.

4. Given by the mouth the extract is ineffective, but fresh gland given by the mouth is stated to be effective (Motzfeldt).

5. Anterior lobe extract has no effect on the secretion of urine.

### III. THE ASSOCIATION BETWEEN DIABETES INSIPIDUS AND DISORDERS OF THE PITUITARY.

In considering the evidence upon this matter, there are obviously three possible abnormal conditions to be looked for, namely, (1) a lesion of the pituitary with, and (2) without, diabetes insipidus; and (3) diabetes insipidus without a lesion of the pituitary. In the discussions of this subject which one finds in the literature there is a considerable tendency to collect only those instances which belong to the first of these three classes.

#### (a) *Lesions of the Pituitary with Diabetes insipidus.*

Various authors have noted the frequent association of diabetes insipidus with pathological conditions in which the pituitary is likely to be affected, namely with fracture of the base of the skull and other forms of head injury (Borszéký (21), Frank (22), Cushing (23), Kleeblatt (10), Finkelnburg (24), Graham (25), French and Ticehurst (26)); syphilitic basal meningitis (Oppenheim (27), Benario (28), Ebstein (29)); bitemporal hemianopsia (Spanbock and Steinhaus (30), though the authors conclude that the association is accidental); and adiposogenital dystrophy (Cushing (31)), and infantilism (Marie and Boutier (32)). In the abstracts from the literature given below we have brought together only those cases in which a lesion of the pituitary was demonstrated by post-mortem examination.

Hagenbach (33), in 1882, described the case of a child, aged  $4\frac{1}{2}$  years, who is stated to have passed as much as 9.8 litres of urine daily. There was tuberculous meningitis with dilatation of the lateral and fourth ventricles; the infundibulum was distended by a caseous nodule in its interior, the remainder of the gland showing no changes. Another instance of tuberculosis of the pituitary is given by Borelli (34). The day's volume of urine exceeded 6 litres during the two months before death. At autopsy, a mass of caseating tissue was found occupying the middle cerebral fossae and sella turcica; this had destroyed the whole of the pars nervosa and pars intermedia, and had invaded about one-fifth of the pars anterior. No lesions within the brain are mentioned. Of Meyenburg's (35) two cases, the first showed destruction of the greater part of the pars nervosa and pars intermedia by tuberculosis, the pars anterior being much less affected; in the second the whole of the gland, with the exception of a small part of the pars anterior, had been replaced by a malignant epithelial tumour. In neither was any lesion found within the brain.

Newmark (36) describes a tumour of uncertain nature lying between the

cerebral hemispheres and occupying and distending the whole third ventricle without invading the brain substance; the pars nervosa and greater part of the pars intermedia of the pituitary had been destroyed by it. There was extreme polydipsia and polyuria, but no details are given of the state of the urine. In Römer's (14) case, in which the anti-diuretic effect of pituitrin was demonstrated, there was a tumour at the base of the brain which had invaded the stalk and posterior lobe of the pituitary, but no adequate account is given of the post-mortem findings.

Berblinger (37) has recorded a case in which the day's volume of urine fell after an operation for cerebral decompression, which resulted in the escape of much cerebro-spinal fluid, from 5 or 6 litres to less than 2 litres, but rose again subsequently. At autopsy a sarcoma was found lying in both frontal lobes and extending into the stalk and posterior lobe of the pituitary. A lengthy account of the tumour is given, but its exact distribution in the pituitary is not very clearly stated. Goldzieher (38) describes two instances of polyuria associated with lesions of the pituitary. In the first the day's volume of urine amounted to 6 litres; there was severe chronic nephritis which may have been to some extent the cause of the polyuria. The pituitary was compressed by a gumma resting on the sella turcica; the stalk and posterior lobe had disappeared completely, their position being occupied by tough scar tissue, while the pars intermedia and anterior lobe showed no distinct histological changes. In the second case (5 to 6 litres urine daily, sp. gr. 1,001) there was primary carcinoma of the lung without metastases within the skull, and chronic interstitial nephritis. The pituitary showed a great multiplication of the colloid cysts of the pars intermedia; these had invaded and replaced the greater part of the posterior lobe, of which only a small portion persisted in a fibrosed state, and extended into the stalk. The anterior lobe showed only an increase of basophil cells. Goldzieher regards the condition as one of adenoma of the pars intermedia.

Parkes Weber and Schmidt (39) describe some unique appearances in the pituitary from a case of diabetes insipidus. The patient suffered from pulmonary and laryngeal tuberculosis, and passed about 10 litres of urine daily. The posterior portion of the pituitary was considerably enlarged, and almost completely surrounded the anterior portion; it was composed chiefly of large granular cells, many of the granules staining with sudan III. The anterior lobe was normal in structure. No evidence of any tuberculous process was found in the pituitary, and no lesion was observed in the brain. The state of the pars intermedia, which is of course not very distinct in the human gland, is not described; since the normal pars posterior does not present any such cellular structure as was present in this case it is possible that the condition was one of adenoma of the pars intermedia (cf. Goldzieher's case, above).

Cushing (23) gives the clinical history of a case in which 'the autopsy disclosed an interpeduncular cystic tumour—the usual squamous epithelial lesion derived from an anlage of Rathke's pouch. The hypophysis was greatly flattened and contained but a few normal cellular elements.'

The metastatic tumours of the pituitary were first described by Simmonds (40), who observed two cases accompanied by diabetes insipidus. The first of these was that of a woman who after removal of the breast for a carcinoma began to suffer from polyuria, passing as much as 19 litres of urine daily; the amount decreased to 4 litres during the last days of life. The pars nervosa was destroyed completely by a nodule of carcinoma, while the remainder of the pituitary, with the stalk, was not invaded. No lesion was found in the brain. The second case was very similar, but in addition the stalk and pars intermedia were permeated by the carcinoma. Simmonds records also a case of diabetes insipidus in which a sarcoma in the region of the third ventricle had extended into the stalk and pars nervosa.

Sekiguchi (41) has published two cases, similar to those of Simmonds, of metastasis of breast carcinoma in the pars nervosa only, without lesions in the brain. Our Case II, and that described by Erdheim (13), were in all probability of the same nature. Other instances of the association of such metastatic tumours with diabetes insipidus are given by Cushing (23) and Fleckseder (42); in the former there was a nodule of lymphosarcoma in the stalk, in the latter the pars nervosa and stalk were replaced by a metastasis of melano-sarcoma. In neither case is any other abnormality within the skull mentioned.

Hijmanns van der Bergh and van Hasselt (43) describe an instance of teratoma of the pineal gland in a boy, who showed sexual precocity and great polyuria. This case has been regarded as indicating a connexion between the pineal gland and diabetes insipidus, but the account of the autopsy shows that there was a metastasis occupying the infundibulum and stalk of the pituitary; the gland itself was somewhat flattened, but showed no histological changes.

We have not had access to the descriptions by Bartels (44) and von Gierke (45) of cases which should be included in this section.

Apparently there is no record in the literature of any metastasis in the pars anterior; possibly its great vascularity (see the figure of an injection in Herring's paper (46)) is unfavourable to the lodgement of cells.

These observations are brought together in the following table, which shows that a morbid change restricted to the infundibulum (1), to the 'posterior lobe' (10?), to the stalk (11), (17), or to the pars nervosa (12), (15), (16), has been found associated with diabetes insipidus.

It is noteworthy that in no case has the pars anterior been completely destroyed, and in all but two cases was not found affected.

The stalk was affected eleven times, the pars nervosa ten times, the pars intermedia seven, and the posterior lobe six.

TABLE IX.

Observer.	Morbid Condition.	Stalk.*	Pars Nervosa.	Pars Inter-media.	Pars Anterior.	'Posterior Lobe.'	Infundibulum.*
1 Hagenbach	tubercular nodule	—	—	—	—	—	+
2 Borelli	tubercular nodule		+	+	$\frac{1}{3}$ +		
3 Meyenburg	tubercular nodule		+	+	—		
4 Meyenburg	tumour	+	+	+	small part—	+	+
5 Newmark	tumour		+	+			
6 Römer	tumour	+				+	
7 Berblinger	tumour	+				+	
8 Goldzieher	gumma	+		—	—	+	
9 Goldzieher	tumour	+		+	—	+	
10 Parkes-Weber and Schmidt	?adenoma			+?	—	+	
11 Cushing	tumour	+					
12 Simmonds	tumour	—	+	—	—	—	—
13 Simmonds	tumour	+	+	+	—	—	—
14 Simmonds	tumour	+	+				
15 Sekiguchi	tumour		+				
16 Sekiguchi	tumour		+				
17 Cushing	tumour	+					
18 Fleckseder	tumour	+	+				
19 van den Bergh	tumour	+					+

+ indicates that part was affected.

— indicates that part was normal.

Blank space indicates that part was not mentioned.

\* We have used the terms 'stalk' and 'infundibulum' as given by each author; there seems to be no very definite difference in meaning between the two, though the 'infundibulum' may include the portion of the brain adjacent to the attachment of the stalk.

(b) *Lesions of the Pituitary without Diabetes Insipidus.*

Simmonds (40) investigated in all ten cases of tumour in the pituitary (eight by metastasis and two by direct extension); of these, three showed polyuria and seven did not. His descriptions of the former have been quoted above; of the latter, he gives details of two only, and these are usually omitted in references to Simmonds's work upon the association of the pituitary with diabetes insipidus. Both were cases of metastasis from carcinoma of the breast; the first was to all appearances identical with one of those described in the preceding section, the pars nervosa, pars intermedia, and stalk being replaced by growth, yet there was no polyuria. The second case is inconclusive and is not adequately described; there was polyuria (4.8 litres per day) in December 1912, which had ceased when the patient next came under observation a year later and did not reappear before her death in January 1914; the whole pituitary, except a part of the pars anterior, had been destroyed by the tumour. A diminution in the amount of urine in the last few days of life has often been noted in diabetes insipidus, but in this case the period was considerably longer.

Eason and Johnson (47) give an account of a large tumour arising in the



pars anterior of the pituitary; no portion of the pars intermedia or pars nervosa was found on microscopical examination, and the patient had shown no polyuria. Among the numerous records of hypophyseal tumours collected by Strada (48) there are two in which the pituitary was completely destroyed, but no mention is made of polyuria, although the urine was tested qualitatively. In Cushing's (23) case of diabetes insipidus after sellar decompression, the gland was found at the operation to be considerably flattened by a tumour above it and fibrosed, but there had been no polyuria. In the absence of an autopsy the exact nature of this case must remain uncertain.

These observations are brought together in the following table:

TABLE X.

Observer.	Morbid Con- dition.	Stalk.	Pars Nervosa.	Pars Inter- media.	Pars Anterior.	'Poste- rior Lobe.'	Infundi- bulum.	Polyuria.
1 Simmonds	tumour	+	+	+				none
2 Simmonds	tumour	+	+	+	partly destroyed			at one period, but not for a year before death
3 Eason	tumour		+	+	+			none
4, 5 Strada	tumour	+	+	+	+	+	+	not mentioned
6 Cushing	gland flattened and fibrosed by tumour pressure, no autopsy							none

+ indicates that part was affected.

Blank space indicates that part was not mentioned.

It is worthy of remark that in three of these cases, 3, 4, and 5, the anterior lobe was affected; this in conjunction with the absence of polyuria might suggest that the polyuria in cases such as those given in Table IX was due to the action of this part of the gland; but the absence of effect upon the urine in extracts of the anterior lobe (Schäfer and Herring (2), Motzfeldt (4)) is against this view.

(c) *Diabetes Insipidus without a Lesion of the Pituitary.*

We have found no record of any case of diabetes insipidus in which abnormality of the pituitary was excluded with certainty by post-mortem examination, if one excepts the one recorded by Götzl and Erdheim (49). In this the volume of urine was from 6 to 9 litres per day; the pituitary was slightly flattened by a tumour in the third ventricle, but showed no other changes (cf. Cushing's case of interpeduncular cystic tumour, included in section (a) above); there was distension of the ventricles and some invasion of the brain substance. The case illustrates the difficulty of drawing any conclusion in these matters from the evidence of morbid anatomy; such pressure from above might well obstruct the passage of secretion from the pituitary into the ventricle. The considerable amount of earlier literature is of little value from the present point of view, as no special attention was paid to the condition



of the pituitary (see for instance the collection of post-mortem findings in cases of diabetes insipidus by Ebstein (29), and the case showing ependymitis of the floor of the fourth ventricle described by Pichler (50)). But it is probable that the more recent literature also does not show the true state of the matter, since, in the light of our present knowledge of the importance of the pituitary, a case of diabetes insipidus in which a lesion of this gland is found at autopsy excites special interest which may lead to publication, while cases in which no such condition is found, though really of equal value, may attract less attention.

It is evident that diabetes insipidus occurs in cases in which disorder of the pituitary, if present at all, must be of a transitory nature, for the condition may appear in pregnancy, cease after delivery, and reappear in subsequent pregnancies. Novak (51) quotes, among other instances of this kind, one in which the amount of water drunk daily fell after delivery from 15 litres to 2 or 3 litres; this polydipsia reappeared in two subsequent pregnancies.<sup>4</sup> It is known that there is an increase in size and weight of the pituitary, with cellular changes, in pregnancy (Erdheim and Stumme (52)); but these cases alone show how defective is the basis of any generalization, such as is laid down at great length by Frank (22) for instance, to the effect that diabetes insipidus is due in every instance to disorder of the pituitary.

It is clear that the whole evidence upon this question which can be obtained from morbid anatomy is inconclusive. Perhaps the chief difficulty is that, within the practically closed cavity of the cranium, the exact range of effect by pressure of a tumour cannot be defined exactly; the anatomical site of an intracranial lesion may not indicate its whole functional importance. However, there are some points in the three sections above which are worth some discussion.

1. The nineteen instances of pituitary tumour with diabetes insipidus given in the first section appear to provide very strong evidence for a connexion between these two conditions until one considers, among others, the case recorded by Simmonds which, while apparently identical anatomically with some of the first series, showed no polyuria. In all such cases where the importance of a ductless gland is in question it is of course easy to suggest that a surviving portion, sufficient in amount to carry on the function of the organ, had escaped observation. Another possible explanation may be considered; it may be that the pituitary is in some persons active, in others inactive, in controlling the secretion of urine; in the latter its destruction will not produce any abnormality. Haliburton, Candler, and Sikes (54) examined the physiological action of extracts of twenty-four human pituitaries, obtained mostly from cases of insanity; the diuretic effect was completely absent in three, and extremely slight in two, of these.

<sup>4</sup> These cases remind one of the remarkable instance of rapidly developing acromegaly in pregnancy, with recession of the anatomical changes after delivery, recorded by Marek (53).

2. In each of the nineteen cases the portion of the pituitary most affected is that composed of the pars intermedia, pars nervosa, and stalk; in three of them only is any definite involvement of the pars anterior described. This is significant in that the diuretic and anti-diuretic effects are exhibited by extracts of the posterior lobe (pars intermedia and nervosa) alone, and not by those of the pars anterior. Further, in some the tumour involved the stalk only, the remainder of the gland being to all appearances unaffected (Hagenbach: Hijmanns van den Bergh; Cushing's case of lymphosarcoma). These might appear to weaken the evidence for the importance of the pituitary in the respect in question, but in view of the probability that the secretion reaches the circulation by way of the stalk (see 'Discussion of Results' below) the occurrence of such cases would be expected, and they are of especial interest and value.

3. As there appear to be no records of autopsies in cases of diabetes insipidus in which the pituitary was examined and found to be perfectly normal, the existing evidence of morbid anatomy seems on the whole to be distinctly in favour of an association between lesions of the gland and the disease in question. But, as was pointed out above, the literature in this respect may not give a true picture of the case; and further, diabetes insipidus occurs in many conditions where post-mortem records in such cases are lacking (e.g. pregnancy, cerebral syphilis, head injuries as in our Case I). It is therefore at present impossible to decide whether disorder of the pituitary is in all cases the cause of the disease.

(d) *Experimental Results.*

1. *Lesions of the pituitary and adjacent portions of the brain.* The investigations in which polyuria has been produced by lesions of the pituitary and of the central nervous system do not lend themselves to classifications on the above lines, and may therefore all be considered together.

Lewis and Mathews (55) give an inadequate account of the experimental polyuria produced by lesions of the pituitary; by far the largest amount of work in this field has been done by Cushing and his fellow-workers (23, 56, 57, 58, 59).

Cushing (23) has discussed the results, but if one examines the protocols there is sufficient irregularity to make it very difficult to provide any summary which is both brief and reliable. Further, it is not easy to decide in all cases whether there was or was not polyuria, owing to variations in the amounts before operation. The following table represents an attempt to collect all the cases of which details are given in the two chief papers (56, 57):

TABLE XI (Cushing).

Operation on Pituitary.	Number of Cases.	Polyuria.
1. Total or nearly total removal	16 (adult dogs)	absent in all
2. Total removal	8 (puppies)	present in most cases, lasting one or two days
3. Removal of anterior lobe alone	3	absent in all
4. Partial removal of anterior lobe	6	present in all
5. Partial anterior with total posterior lobe removal	13	present in 10
6. 'Stalk separation,' (Division of infundibular attachment without removal)	5	present in 4
7. Removal of posterior lobe alone	6	considerable in 3, distinct in 2

The table shows (1) that polyuria occurs in the great majority of cases of removal of the posterior lobe, or of separation of it from the brain (5, 6, 7); (2) that it does not occur after removal of the whole gland in adults, or of the anterior lobe alone (1, 3). It may seem remarkable that removal of the whole gland should not have the diuretic effect which follows removal of the posterior part of it; one must remember that adult dogs do not survive loss of the whole gland or anterior lobe for more than one to five days, which suggests that the absence of effect upon the secretion of urine may be due to incipient failure of vital activity. In accordance with this, puppies (2) which survive total removal longer (up to three weeks) may show polyuria. The polyuria following partial removal of the anterior lobe (4), which is much less rapidly if at all fatal, would seem then to be due to the concomitant disturbance of the posterior lobe. Of these various lesions 'the clean-cut posterior lobe removals elicit polyuria with the greatest regularity' (Cushing).

In these cases the volume of urine is increased as a rule about fourfold, and returns to the normal amount within a few days, but both the amount and duration of the polyuria are very variable (*vide* the curves in Cushing's summary (23)). Thus the volume may be increased on the first day as much as twenty-fold, and in one case (No. 34) considerable polyuria persisted after stalk-separation until the animal was killed six months later. It is these more lasting effects which are of most interest in considering the nature of diabetes insipidus. Such results were obtained only after division of the stalk, but do not by any means invariably follow this operation (56). When such lesions are found to produce in one case a slight polyuria lasting a few days, and in another a considerable polyuria lasting six months, it seems clear that there must be some very important factor which has not yet been determined.

Cushing records other remarkable observations, though these raise rather than answer questions. (1) Transplantation of the entire gland to the cerebral cortex is followed by persistent polyuria, which ceases on removal of the graft; it is difficult to suggest any explanation of the effect of the second operation which is consistent with the results given in the table above, since a fragment of the anterior lobe sufficient to maintain life had been left *in situ* at the first operation. The statements in the two papers (23, 58) as to grafts of the posterior

lobe alone are not consistent. (2) Stimulation of the superior cervical ganglion is followed by glycosuria (Cushing, Jacobson, and Weed (59)), and strong evidence was obtained that this effect is due to a discharge of secretion from the pituitary; since this glycosuria is accompanied by polyuria (23) it was considered probable that the diuretic effect is likewise due to activity of the gland. This line of investigation should be of especial value since it involves no possibility of injury to any part of the brain (cf. the work of Camus and Roussy, below). (3) One may mention here Cushing's remarkable case of extreme polyuria in a woman following the operation of sellar decompression for pituitary tumour (23). There seems to have been no possibility of surgical injury to the brain, but the effect upon the whole cranial contents of relief of great tension must remain doubtful.<sup>5</sup>

Cushing seems to have regarded the view that injury to adjacent portions of the brain might be of importance as not worthy of much notice. The experiments next to be described led to the conclusion that such injuries were the sole cause of these polyurias.

Camus and Roussy (60) performed a number of experiments on dogs, and drew from these the emphatic conclusion that '*la lésion qui détermine la polyurie n'intéresse en aucune manière l'hypophyse. . . L'ablation totale de l'hypophyse, faite sans léser la base du cerveau (infundibulum), ne donne pas de polyurie.*' When one examines the protocols, one finds that these statements are based upon the following results: (1) absence of polyuria after total hypophysectomy in one dog in which no injury of the stalk, infundibulum, or brain was found at autopsy; (2) occurrence of polyuria after total hypophysectomy in five dogs in which the stalk was destroyed or the infundibulum injured, though the infundibulum is described merely as '*dilaté*' or '*altéré*' in some of these; (3) in two dogs recurrence of polyuria, after subsidence of that due to a previous hypophysectomy, when a fresh lesion was produced in the one case in the region of the infundibulum, in the other in that of the tuber cinereum and corpora mammillaria. These are perhaps the most striking experiments, since the polyuria, which was of the same type as that which follows hypophysectomy, was produced in the absence of the pituitary. The interval between the two operations was 17 days in the one case and 42 days in the other. (4) Polyuria in five dogs in which a puncture was made, apparently in the immediate neighbourhood of the infundibulum, without injury to the pituitary; the account of the lesions of the brain found at autopsy is by no means easy to follow, but the conclusion drawn is that '*l'étendue de la zone dont la lésion détermine la polyurie paraît limitée à la région opto-pédonculaire*';<sup>6</sup> *elle siège au niveau de la substance grise du tuber cinereum, au voisinage de l'infundi-*

<sup>5</sup> Finkelnburg (24) also describes a case of diabetes insipidus arising after cerebral decompression; both lateral lobes of the cerebellum and the left lateral ventricle were punctured. The nature of the case is doubtful, as there was no autopsy.

<sup>6</sup> i.e. the area enclosed by the optic tracts and cerebral peduncles, the interpeduncular space.

bulum'. No polyuria followed punctures of the brain either in front of or behind this region (i. e. at the optic chiasma or in the pons).

The polyuria produced in these experiments is considerable, amounting at its maximum to an eight or even ten-fold increase (as much as 5 litres per day in a dog of 13 kg.), and lasting from four to six days. In one case it persisted for six weeks; the autopsy at a later date showed 'infundibulum très dilaté, pas de tige . . . hypophyse petite', i. e. a 'stalk separation' had been carried out, which lesion was found by Cushing to be the most effectual in causing a persistent polyuria.

It is extremely difficult to make any satisfactory comparison of the apparently conflicting results of Cushing and of Camus and Roussy; every detail in the description of each operation and autopsy is of importance; many of the protocols of Camus and Roussy are very scanty, and these workers made a special search for lesions which Cushing seems to have regarded as of no importance. However, it is difficult to believe that the investigations are really as contradictory as they appear, and one may take the various results of Camus and Roussy set out above and consider them in the light of the views of Herring (46) and Cushing.

In the case of (1) above (see p. 248) there is agreement, but in that of (2) there is not; however, any comparison of the total hypophysectomies is difficult, since this operation in the hands of Camus and Roussy seems to have had no rapidly fatal effect such as was observed in adult dogs by Cushing. The results under (3) might be explained by supposing that the second lesion liberated pituitary secretion (see under 'Discussion of Results', below) still retained in the brain and scar tissue at the site of the first operation. Similarly with regard to (4), the 'hyaline bodies' of Herring, which may represent the internal secretion of the pars intermedia, seem to have a remarkable power of movement in the brain substance; it may be that they permeate the whole neighbourhood of the infundibulum, and are liberated into the ventricle by a puncture here. No great value is claimed for these suggestions; in the light of the results obtained by Stahler (see below) it is impossible to deny that a portion of the brain may have a considerable influence upon the secretion of urine independently of any immediate connexion with the pituitary.

2. *Lesions of other portions of the brain.* Polyuria has been produced by lesions of the brain so diverse in situation (sigmoid gyrus of the cerebrum, middle lobe of the cerebellum, medulla and adjacent part of the pons) that the results collectively fail to show any localized control of the secretion of urine. The state of diuresis following punctures of the medulla (Bernard (61), Eckhard (62), Finkelnburg (24), Jungmann and Meyer (63)) lasts for a few days only; attempts to decide by section of the splanchnics whether the nervous paths concerned in this polyuria lie in these nerves have given contradictory results (Eckhard, Jungmann and Meyer), as might be expected from the inevitable effect upon the general arterial pressure. Cushny (64),



in a discussion of this subject, concludes that the puncture polyuria is due to disturbance of the vaso-motor centres controlling the kidney, but the work of Cushing, Jacobson, and Weed mentioned below suggests an entirely different mode of action.

The only experiments of this class in which any imitation of a persistent diabetes insipidus has been produced are those of Stahler (65). Operating upon rabbits by the method employed by Bernard and Eckhard, he was able by punctures of various portions of the medulla and middle lobe of the cerebellum to produce an increase in the volume of urine to about double its previous amount, this condition persisting for three or four days. In order to produce a more lasting irritation, he then resorted to injections of silver nitrate, and in three cases produced very distinct polyuria which continued, with gradual subsidence, for about a month; the maximum increase observed amounted to about fourteen times the normal day's amount. The effects were therefore similar in amount and duration to those obtained in a few cases by Cushing and Camus and Roussy. The only region of injury common to all the successful experiments lay in the position of the nucleus of Deiters and the internal restiform body, but, as Stahler admits, sufficient experiments were not performed to prove that no such result could be obtained by a lesion of any other point.

The question under discussion appears still more complex when it is thus demonstrated that a persistent polyuria can be produced also by lesions remote from the pituitary, but the work of Cushing, Jacobson, and Weed (59) alluded to above upon Bernard's diabetic puncture shows that it may be possible to simplify the matter. They carried out numerous experiments which indicated that the glycosuria following the puncture of the medulla was due to a discharge of pituitary secretion; the whole path of the nervous impulses concerned was not determined, but they pass from the spinal cord to the superior cervical ganglion and thence by post-ganglionic fibres to the pituitary. Since the glycosuria produced by stimulation of this ganglion is generally accompanied by considerable diuresis, it is clearly possible that the polyuria produced by lesions of the medulla is also due to activity of the pituitary, though this explanation must be regarded as distinctly conjectural.

In considering the whole of these experimental results, one inherent difficulty in interpretation is at once apparent. An extract of the pituitary can produce both diuretic and anti-diuretic effects (see under II, above), this double action being attributed to the presence of two substances. One cannot therefore take either an oliguria or polyuria which may follow an experiment as unequivocal evidence of either excess or defect of activity on the part of the gland. Obviously, by suitable assumption of excess or defect of diuretic or anti-diuretic action one could explain any result, but such interpretation would be of no value. One can, however, consider in each case what is the most probable explanation; for instance, a persistent polyuria following stalk separation is not likely to be due to excess of the diuretic substance, nor is such excess likely to be the cause of



a diabetes insipidus in which pituitary extract is beneficial. The following table is put forward merely as an attempt to classify the points upon which we have no certain information :

Condition.	State of Secretion of Urine.	Possible Explanation.
Diabetes insipidus (when due to lesion of pituitary)	} persistent poly- uria	} lack of anti-diuretic substance
Stalk separation		
Posterior lobe removal	} transient poly- uria	} ?
Lesion of medulla oblongata	} polyuria	} secretion of diuretic, or inhibition of secretion of anti-diuretic, substance
Stimulation of sup. cervical ganglion		
Injection of pituitary extract	• polyuria followed by oliguria	successive action of two substances
Removal of engrafted pituitary	diminution of polyuria	?
Total hypophysectomy in adults	oliguria in some cases	failure of vital activity

It is the great differences in the duration of these polyurias which constitute the chief difficulty in interpretation. It is hard to provide any scheme which will cover (1) a twenty-fold increase of urine lasting two days only after removal of the posterior lobe (see Fig. 2 in Cushing's paper (23)), (2) a polyuria persisting throughout the life of the patient in association with a tumour in this same portion of the gland: the prompt restoration of the normal volume of urine in the first of these instances is especially puzzling. It is true that polyurias lasting from one to six months have been produced by artificial lesions, but such results are attained exceptionally and by chance, and thus provide no conclusive evidence as to the causation of diabetes insipidus. One must admit that experimental investigation has not yet given any clear picture of the part played by the pituitary in regulating the secretion of urine under either normal or pathological conditions.

#### IV. DISCUSSION OF RESULTS. THE MECHANISM OF ACTION OF THE PITUITARY UPON THE KIDNEY.

One may here consider three questions: (1) whether it has been proved that the pituitary actually plays a part in the normal body in controlling the secretion of urine; (2) the route by which this influence is exerted; (3) the nature of the action, whether direct or indirect, of pituitary extract upon the kidney.

1. In view of the facts given under II, above, as to the effect of pituitary extract upon the secretion of urine, any doubt upon this point may seem rather superfluous. But it is by no means safe to infer that the functional importance of an organ is demonstrated by the properties of an extract of it; if one applies such an argument to the galactagogue substance in the pituitary of a fish, the absurdity is obvious. The evidence of morbid anatomy and of experimental physiology is inconclusive. Certainly the rapid return of the urinary flow to

within normal limits after the polyuria following total removal of the posterior lobe (see Figs. 3 and 4 in Cushing's paper (23)) shows that the gland is by no means indispensable for the regulation of the kidney's activity; but the fact that it can be dispensed with does not, of course, show that it is normally inactive. Perhaps the strongest argument in favour of the normal activity of the pituitary in this respect is afforded by the effect of the extract in cases of diabetes insipidus. One may perhaps quote Hoppe-Seyler's comment (7) upon this feature in his case: '... es fehlte nur das bischen Pituitirin um normale Verhältnisse zu schaffen.' This remark is very suggestive; when one observes the immediate return to normal conditions after injection of the extract, as in our Case II, it is difficult to avoid the conclusion that one has supplied, not merely some beneficial drug, but the actual substance that was lacking, and that the abnormality consisted wholly in this deficiency.

2. Herring (46) described appearances which suggested that a substance (the 'hyaline bodies') produced in the pars intermedia passed through the pars nervosa and endyma into the third ventricle, and put forward the view that the internal secretion of the pars intermedia was discharged in this way. These histological observations have been confirmed by Crowe, Cushing, and Homans (56), Halliburton, Candler, and Sikes (54), and Atwell and Marinus (79). In support of the direction of motion of these bodies assumed by Herring, it is noteworthy that they accumulate in the pars nervosa after division of the stalk (56), and appear in the brain tissue around a pituitary engrafted in the cerebral cortex (58). Cushing and Goetsch (66) and Cow (67) have examined the cerebro-spinal fluid for the presence in it of the active principles of the pituitary, and obtained results which were considered to demonstrate this; diuresis, after intravenous injection of the fluid, was observed in both these investigations.

The evidence from autopsies in cases of diabetes insipidus at least indicates that integrity of the junction between pituitary and brain is of special importance in the maintenance of normal conditions; and the readiness with which mere division of the stalk, an operation which should not interfere with the blood-supply of the posterior lobe (56), produces polyuria would be difficult to explain if the internal secretion passed directly into the blood-stream.

Lastly, one may consider an *a priori* argument in favour of this process of secretion into the third ventricle: it is hard to see why the remarkable developmental process by which an upgrowth from the buccal epithelium is brought into intimate contact with a portion of the brain should be carried out if there is not to be some transference, in one or other direction, between these two elements.

3. The earlier investigations of the mode of action of pituitary extract upon the kidney sought an explanation of the diuretic effects which were then under observation, and were concerned with alterations in blood-pressure and with vaso-dilator and vaso-constrictor effects upon the renal and other vessels. Schäfer and Herring (68) found that a diuresis might appear together with a fall in arterial pressure and shrinkage of the kidney, and concluded that a 'specific stimulation of the renal epithelium must occur'. Since the recognition of the

anti-diuretic action Motzfeldt and Rees have attempted to find the means by which this effect is produced.<sup>7</sup>

Motzfeldt (3, 4) found no constant alteration in arterial pressure during the period of diminished secretion. By section of the splanchnic or renal nerves he was led to the conclusion that the anti-diuretic effect was due to vaso-constriction in the kidney, but the results are admitted to be inconstant and are by no means convincing.

Rees (6) noticed that injection of pituitary extract in cats frequently caused vomiting, the greater part of any water given shortly before the injection being returned from the stomach, while in rabbits treated similarly the faeces become semi-fluid. These facts suggest that the anti-diuretic effect was due to delayed absorption of water from the alimentary canal, and the following experiments were carried out to test this explanation: (1) in decerebrate dogs, diuresis induced by the intravenous administration of normal saline was not affected by subcutaneous injection of pituitary extract, whereas if the saline were introduced into the stomach the injection caused the usual delay in excretion (see above, p. 239). This would, of course, indicate that the extract affects absorption from the alimentary canal, but it is very unfortunate that the numerical results of these experiments are not given; moreover, Motzfeldt found that pituitary extract checked the diuresis produced by normal saline, given in this case subcutaneously, in the usual manner. (2) The small intestine of animals was exposed, washed, and ligatured at either end after introduction of water.

		c.c. water		Time allowed for Absorption.
		introduced.	recovered.	
Cat	Control	30	8	} 1 hour
	1 c.c. pituitary extract <i>sub cutem</i>	30	27	
Rabbit	Control	30	0	} not stated
	0.5 c.c. pituitary extract <i>sub cutem</i>	30	25	
Decerebrate dog				
Control		75	42	} half an hour
	' Injected period '	75	70	

These three experiments show a great diminution in the rate of absorption of water from the intestine, but they do not by any means demonstrate, as Rees seems to consider, that this diminution is either the direct action of the pituitary extract or the cause of the lessened flow of urine. Konschegg and Schuster (5) (see under II, above) found that the water content of the blood was raised by 2 per cent. during the period of diminished secretion. At first sight the results of Rees and of Konschegg and Schuster appear contradictory, since there is in the one case a withholding of water from the blood and in the other an accumulation

<sup>7</sup> Grundmann has devised a theory of diabetes insipidus which involves a number of ductless glands and portions of the nervous system sufficient to explain almost any abnormality; the theory is not adapted to abbreviation, or even to comprehension, so one may refer to the original (20).

of water in it. But it may be that the intestinal epithelium is sensitive, as is the kidney, in regulating the composition of the blood, and that when a state of hydraemia is developing, as in Korschegg and Schuster's experiments, this epithelium, as it were, abstains from adding any more water to the blood although the pituitary extract may have no direct action upon it. It is obvious that diminished absorption from the alimentary canal cannot be the cause of the lessened formation of urine if the blood is at the same time more dilute. Simultaneous estimations of the rate of absorption from the gut, the water content of the blood, and the flow of urine would show whether the different observations can be reconciled in this way.

It has also been suggested (Abrahamson and Climenko (69)) that the pituitary affects the formation of urine, not by any action upon the kidney, but by regulation of the salt content of the tissues. But the dilution of the blood observed by Korschegg and Schuster can scarcely be explained in any other way than by a primary effect upon the kidney. This effect may be vaso-motor in nature, although experiments in this direction have been inconclusive; or may consist in a direct influence upon the secretion or reabsorption of water by the cells of the kidney; in our ignorance of the normal process of formation of urine there is, of course, no basis for discussion of these possibilities. It is very desirable that the observations of Korschegg and Schuster upon the retention of water should be confirmed in other cases.

Recently Knowlton and Silverman (78) have shown that the diuresis produced by pituitary extract, in contrast to that following injection of urea and sodium sulphate, is not accompanied by any increase in the amount of oxygen consumed by the kidney. They conclude that the diuresis is brought about wholly by increased blood-flow through the kidney, and is not due to activity of the renal cells.

#### V. SOME METHODS OF TREATMENT IN DIABETES INSIPIDUS.

Anti-syphilitic treatment would be employed where indicated by a positive Wassermann reaction or other features of the case. Examples of the results, which may be very striking, are given by Benario (28) and Ebstein (29). In Benario's case E. M., in which there was a positive Wassermann reaction without any history or signs of genital infection, the day's volume of urine fell from seven litres to within normal limits during a month's treatment.

The most effectual treatment in other cases is, of course, the subcutaneous injection of pituitary extracts; the results to be expected have been described above (Case II, and under II *b*). The obvious disadvantage of this method is the necessity for daily repetition of the injection; instances in which a lasting effect has been ascribed to the treatment (Graul (11)) are no doubt to be explained by the independent recovery of the patient, as in our Case I. In Case II the subcutaneous injection of 1 c.c. of pituitirin produced a practically normal condition of the urine lasting about six hours, the beneficial effect being moreover still

distinct during the next six-hour period (Table IV). If then an injection were given at bed-time, an uninterrupted night's rest should be secured; time must be allowed for the action of the bowels which may occur. There seems to be no danger of any considerable rise of blood-pressure following injection of amounts sufficient for the purpose in question; in Motzfeldt's numerous observations (4) the effects upon blood-pressure were very variable, a fall occurring more often than a rise.

Where the continuance of daily injections is not practicable or desirable, other methods must be considered. There seems to be no prospect of success in the administration by the mouth of any of the existing commercial preparations (see II *b*, above). Where the material was obtainable, the use of the cooked fresh glands, stated by Motzfeldt to be effectual, could be tried. A reduction in the amounts of protein and salt in the diet may or may not reduce the volume of urine; in Case II the effect was distinct but very transient. Minkowski (74) has observed that such modification of the diet may be very beneficial, or of no service, in cases apparently similar. But some restriction of the intake of salt would seem to be in all cases advisable (see Table VI). As would be expected, a great variety of drugs has been employed in this disease (Futcher (75)). Umber (76) describes good results from the use of strychnine. Formerly ergot was thought to be of considerable value (Da Costa (77), quoted by Newmark (36)). This is of some interest since Motzfeldt (3) found that a preparation of ergot had an inhibitory effect upon diuresis in rabbits like that of pituitary extract. He obtained similar results with some amines ( $\beta$ -iminazoethylamine, *p*-oxyphenylethylamine); possibly the anti-diuretic substance of the pituitary is a simple amine of this nature.

#### *Summary.*

1. Data are given as to the composition of the urine, and its molecular concentration in comparison with that of the serum, in two cases of diabetes insipidus. When large amounts of sodium chloride are given, the diuresis is so adjusted that the percentage of nitrogen plus chlorine in the urine remains unaltered; the kidney, therefore, lacks the power of concentration which is exhibited normally after ingestion of salt.

2. The anti-diuretic effect of pituitary extract given by subcutaneous injection was demonstrated both in a normal subject and in a case of diabetes insipidus; administration of such preparations by the mouth is ineffectual.

3. No record has been found in the literature of any case of diabetes insipidus in which abnormality of the pituitary was excluded with certainty by post-mortem examination, whereas in a considerable number of cases the disease has been associated with a lesion of the posterior lobe of the gland. However, such lesions are not invariably accompanied by diabetes insipidus. The evidence of morbid anatomy as to a connexion between the pituitary gland and diabetes insipidus is therefore inconclusive.

4. The experiments of Cushing have shown that polyuria can be produced



experimentally by lesions of the posterior lobe of the pituitary, but the great variations in the duration (two days to six months) of these polyurias show that there is some very important factor which has not yet been determined. The polyuria produced by lesions of the brain adjacent to the pituitary (Camus and Roussy) may perhaps be accounted for by the diffusion of pituitary secretion in the brain substance. There is also some evidence that the polyuria following stimulation of other parts of the nervous system (medulla, superior cervical ganglion) is due to activity of the pituitary.

5. The anti-diuretic effect of pituitary extract appears to be due to direct action upon the kidney (Konschegg and Schuster); the experiments of Rees do not demonstrate that it is the result of diminished absorption from the intestine.

6. The immediate restoration of a normal state of the urine when pituitary extract is given in diabetes insipidus provides the strongest evidence for the normal activity of the gland in regulating the secretion of urine.

In conclusion, we wish to express our thanks to Dr. W. Essex Wynter and Mr. T. H. Kellock for the facilities which have been afforded us in investigating these cases.

## REFERENCES.

1. Magnus and Schäfer, *Journ. Physiol.*, Lond., 1901, xxvii, Proc. ix.
2. Schäfer and Herring, *Proc. Roy. Soc.*, B. 1905-6, lxxvii. 571.
3. Motzfeldt, *Journ. Exper. Med.*, New York, 1917, xxv. 153.
4. Motzfeldt, *Boston Med. and Surg. Journ.*, 1916, clxxiv. 644.
5. Konschegg u. Schuster, *Deutsch. med. Woch.*, 1915, xli. 1091.
6. Rees, *Amer. Journ. Physiol.*, 1918, xlv. 471.
7. Hoppe-Seyler, *Münch. med. Woch.*, 1915, lxii. 1633.
8. Rosenfeld, *Berlin. klin. Woch.*, 1916, liii. 553.
9. Farini, *Gazz. degli Osped.*, 1913, xxxiv, ii. 1135, abstract in *Brit. Med. Journ.*, Epitome 76, 1913.
10. Kleeblatt, *Med. Klinik*, 1915, xi. 915.
11. Graul, *Deutsch. med. Woch.*, 1915, xli. 1095.
12. Orlandi, *L'Osped. Maggiore, Milano* (1914), No. 9, abstract in *Zentralblatt für Biochem. u. Biophys.*, 1915, xviii. 161.
13. Erdheim, *Wien. klin. Woch.*, 1914, xxvii. 867.
14. Römer, *Deutsch. med. Woch.*, 1914, xl. 108.
15. Miller, *Amer. Journ. Med. Sci.*, 1916, clii. 549.
16. Barker and Mosenthal, *Trans. Assoc. Amer. Physicians*, 1917, xxxii. 233.
17. Barker and Hodge, *Endocrinology*, 1917, i. 427.
18. Rosenbloom, *Journ. Amer. Med. Assoc.*, 1918, lxx. 1292.
19. Williams, *Endocrinology*, 1917, i. 312.
20. Grundmann, *Berlin. klin. Woch.*, 1917, liv. 743.
21. Borszéký, *Beitr. z. klin. Chirurg.*, 1901, xxxi. 716.
22. Frank, *Berlin. klin. Woch.*, 1912, xlix, i. 393.
23. Cushing, *Boston Med. and Surg. Journ.*, 1913, clxviii. 901.
24. Finkelnburg, *Deutsch. Archiv f. klin. Med.*, 1907, xci. 345, and 1910, c. 33.
25. Graham, *Ann. of Surg.*, 1917, lxi. 529.
26. French and Ticehurst, *Trans. Clin. Soc.*, Lond., 1906, xxxix. 117.
27. Oppenheim, *Nothnagel's Spec. Path. u. Therap.*, Bd. ix. 'Die syphilitischen Erkrankungen des Gehirns', 53, Wien, 1896.



28. Benario, *Munch. med. Woch.*, 1913, lx. 1768.
29. Ebstein, *Deutsch. Archiv f. klin. Med.*, 1909, xcv, i.
30. Spanbock u. Steinhaus, *Deutsch. med. Woch.*, 1898, xxiv. 828.
31. Cushing, *Amer. Journ. Med. Sci.*, 1913, cxlv. 813.
32. Marie and Boutier, *Revue neurol.*, Paris, 1913, xxv. 555.
33. Hagenbach, *Jahrb. f. Kinderheilkunde*, 1883, xix. 214.
34. Borelli, *Giorn. della R. Accad. di Med.*, Turin, 1913, lxxvi. 91, abstract in *Brit. Med. Journ.*, Epitome 65, 1913.
35. Meyenburg, *Beitr. z. path. Anat. u. allg. Path.*, 1916, lxi. 550.
36. Newmark, *Arch. Int. Med.*, 1917, xix. 550.
37. Berblinger, *Verhand. der Deutsch. path. Gesell.*, 1913, 273.
38. Goldzieher, *ibid.*, 281.
39. Parkes Weber and Schmidt, *Amer. Journ. Med. Sci.*, 1916, clii. 892.
40. Simmonds, *Munch. med. Woch.*, 1913, lx. 127, and 1914, lxi. 180.
41. Sekiguchi, *Ann. of Surg.*, 1916, lxiii. 297.
42. Fleckseder, *Wien. klin. Woch.*, 1914, xxviii. 867.
43. Hijmanns van den Bergh and van Hasselt, *Nederlandsch Tijdschrift voor Geneeskunde*, 1913, lvii. 1271.
44. Bartels, *Zeitschr. f. Augenheilkunde*, 1906, xvi.
45. von Gierke, *Verhand. Deutsch. path. Gesell.*, 1914, xvii. 200.
46. Herring, *Quart. Journ. Exper. Physiol.*, 1908, i. 121.
47. Eason and Johnson, *Guy's Hospital Reports*, 1914, lxxviii. 65.
48. Strada, *Virchow's Archiv*, 1911, cciii. 1.
49. Götzl u. Erdheim, *Zeit. f. Heilkunde*, 1905, xxvi, *Abt. f. inn. Med.*, 372.
50. Pichler, *Zentralbl. f. inn. Med.*, 1903, xxiv. 745.
51. Novak, *Berlin. klin. Woch.*, 1917, liv. 107.
52. Erdheim and Stumme, *Beitr. z. path. Anat. u. allg. Path.*, 1909, xlv. 1.
53. Marek, *Zentralblatt f. Gynaek.*, Leipzig, 1911, xxxv. 1612.
54. Halliburton, Candler, and Sikes, *Quart. Journ. Exper. Physiol.*, 1909, ii. 229.
55. Lewis and Mathews, *Trans. Path. Soc.*, Chicago, 1913, ix. 16.
56. Crowe, Cushing, and Homans, *Johns Hopkins Hosp. Bull.*, 1910, xxi. 127.
57. Cushing, Goetsch, and Jacobson, *ibid.*, 1911, xxii. 165.
58. Crowe, Cushing, and Homans, *Quart. Journ. Exper. Physiol.*, 1909, ii. 389.
59. Cushing, Jacobson, and Weed, *Johns Hopkins Hosp. Bull.*, 1913, xxiv. 40.
60. Camus and Roussy, *Compt. rend. de la Soc. de Biol.*, 1913, lxxv. 483 and 628; 1914, lxxvi. 121, 773, and 877.
61. Bernard, *Leçons de physiologie expérimentale*, Paris, 1855, p. 339.
62. Eckhard, *Beiträge z. Anat. u. Physiol.*, Giessen, 1869, iv. 1, and 1872, vi. 55.
63. Jungmann u. Meyer, *Arch. f. exp. Path. u. Pharm.*, 1913, lxxiii. 49.
64. Cushny, *The Secretion of Urine*, Lond., 1917.
65. Stahler, *Prager Zeitschr. f. Heilkunde*, 1886, vii. 105.
66. Cushing and Goetsch, *Amer. Journ. Physiol.*, 1910, xxvii. 60.
67. Cow, *Journ. Physiol.*, Lond., 1915, xlix. 367.
68. Schäfer and Herring, *Phil. Trans. Roy. Soc.*, B. 1908, excix. 1.
69. Abrahamson and Climenko, *Journ. Amer. Med. Assoc.*, 1917, lxix. 281.
70. von der Velden, *Berlin. klin. Woch.*, 1913, l. 2, 2083.
71. Macallum and Benson, *Journ. Biol. Chem.*, 1909, vi. 87.
72. Meyer, *Deutsch. Archiv f. klin. Med.*, 1905, lxxxiii. 1.
73. Schmidt, *Charakteristik der epidemischen Cholera*, Leipzig, 1850.
74. Minkowski, *Therap. d. Gegenw.*, Berlin, li. 4, 1910.
75. Futeher, *Johns Hopkins Hosp. Reports*, 1902, x. 197.
76. Ueber, *Ernährung u. Stoffwechselkrankheiten*, Berlin, 1909.
77. Da Costa, *Med. News*, 1882.
78. Knowlton and Silverman, *Amer. Journ. Physiol.*, 1918, xlvii. 1.
79. Atwell and Marinus, *ibid.*, xlvii. 76.
80. Addis, Barnett, and Shevsky, *ibid.*, xlv. 52.

## THE FILTER-PASSING VIRUS OF INFLUENZA

By JOHN ROSE BRADFORD, E. F. BASHFORD, AND J. A. WILSON

TOGETHER WITH AN APPENDIX OF CLINICAL NOTES ON THE  
CASES OF INFLUENZA FROM WHICH THE VIRUS WAS  
RECOVERED,

By F. CLAYTON

With Plates 16-22

### INTRODUCTION

By JOHN ROSE BRADFORD

IN the last number of this Journal the results of an inquiry into the nature of acute infective polyneuritis were published and the causative organism of the disease described and figured. This work became the starting-point of an inquiry of much wider scope, having as its object the study of a number of diseases hitherto of doubtful or of unknown aetiology.

This work was carried out in the laboratories attached to certain hospitals, No. 20 and No. 26 General Hospitals in the Étaples area of the British Expeditionary Force. In the paper on polyneuritis it was shown that the organism causing this disease possessed certain resemblances to that described by other observers as the cause of poliomyelitis, and the conclusion was reached that the polyneuritis results tended to show that the organisms of poliomyelitis and of polyneuritis were different members of one group. In other words, the poliomyelitis organism was not a peculiar and unique organism; there might be others allied to, but not necessarily identical with it.

The clue to the unravelling of the nature and aetiology of polyneuritis had been afforded by the comparison of the clinical picture of the palsy of polyneuritis with that of experimental paralytic rabies.

In the light of these facts, it was natural for the investigation to be now directed with a wider outlook, and for the method that had proved successful in polyneuritis to be applied to other diseases. Further, inasmuch as rabies had afforded the first clue, it was natural in the first instance to make an attempt to determine the exact nature of the virus of this disease, especially as there were reasons for supposing that this virus might belong to the group of 'filter-passers'. Recently, other observers had shown that the virus of trench

fever belonged to this group; hence, as soon as material could be obtained, a series of observations were made on rabies and on trench fever, and successful results obtained. The full details of this work will be published as soon as practicable. Inasmuch as the methods of culture and of experiment had now proved successful in maladies where there were reasons for thinking that the virus was a true filter-passer, it seemed probable that it might be applicable more generally to other maladies reputed to be due to such organisms, and to maladies the causation of which was quite obscure. A considerable number were investigated on these lines, and successful results obtained in many, including nephritis, encephalitis, and certain of the exanthemata that were available for examination. In October 1918 the problem of influenza was attacked, and a filter-passing virus successfully grown from the blood in certain cases of acute and severe influenza. Since then much experimental work has been done on a number of diseases of obscure and doubtful aetiology, and it is hoped that the results obtained will be published in due course as a series of papers, each dealing with an individual disease and recording the work done in the Étapes area. The present communication deals only with the results obtained in the study of influenza. A preliminary report, containing a mere summary of the results in trench fever, nephritis, and influenza, was published in the *British Medical Journal* and *Lancet* of February 1, 1919. In this report a short description of the organisms isolated in these diseases was given, and further it was definitely stated that inoculation of the cultures of the respective organisms reproduced in animals illness and the lesions characteristic of the maladies, i. e. nephritis and influenza. Finally, that the organism in question could be recovered from such experimental animals, or in the case of trench fever from man. Thus, in respect of the diseases considered in the preliminary report the conditions ordinarily known as Koch's postulates were fulfilled. The present communication gives for influenza the full details of the cultural and experimental facts on which this statement in the preliminary report is based. The similar facts in regard to nephritis, encephalitis, and trench fever will be published later.

Three outbreaks of influenza or of reputed influenza have occurred amongst the troops of the British Expeditionary Force. The first occurred in the spring of 1918, the second in the autumn of 1918, and the third in the early months of 1919. The investigations on which this communication is founded dealt only with the second and third outbreaks of the disease. These two outbreaks were not only widespread, involving very large numbers of men, but they were also of a severe type, and this is more especially true of the epidemic of 1918. The cases in the autumn of 1918, and those in the spring of 1919, were essentially of the same character, and reproduced all the features of the disease familiar to those whose clinical experience had enabled them to have seen the former epidemics in England of 1890 and 1891. The epidemic in the spring of 1918 may have been pure influenza of a mild type, but it presented considerable differences in its clinical course to that seen in the subsequent epidemics in the autumn and following spring. Three facts in particular stand out in reference to the

epidemic of the spring of 1918: the extraordinarily low mortality, the infrequency of pulmonary complications, and the remarkable frequency with which the fever subsided by crisis on the third or fourth day of illness. It may be that the anomalous clinical course was due to the infection being a mild one, but it is unfortunate that the technique used in our work could not be applied to the investigation of the first epidemic. At the date when this epidemic occurred, polyneuritis was the only disease in which this method was employed, and thus we have no facts as to the presence of the true filter-passing virus of influenza in this first epidemic. As regards the other two epidemics, the results obtained by us were the same in both.

*Influenza as seen in the B.E.F. in the Epidemics of the Autumn of 1918 and the Early Spring of 1919.*

Both these epidemics, but more especially the first, were characterized by the frequency and the severity of the pulmonary lesions. These, in many instances, were complications in the true sense of the word, in that they were due to secondary infections; but in other cases, and by no means the least interesting, they were not really true complications, but were lesions dependent upon the pathogenic action of the filter-passing virus of influenza itself.

The pulmonary lesions associated with severe influenza may be divided broadly into four groups according to the character of the dominant lesion present: (1) Bronchitis, (2) Pneumonia, (3) Haemorrhagic oedema of the lung, (4) Pleural effusion. Some of these lesions are obviously true complications, although they may present features both clinically and anatomically slightly different to those seen when they arise apart from influenza. Others present characteristic features that seem to be specific of influenza.

(1) *Bronchitis.* The bronchitis associated with influenza has often been of a severe purulent type, with a nummulated green sputum presenting resemblances to the remarkable disease that was prevalent amongst the troops in the autumns of 1914 and 1916. This malady was characterized by an abundant greenish nummulated sputum, associated with an illness of prolonged duration, i.e. several weeks accompanied with high fever. It is remarkable that at the periods when this malady was prevalent, i.e. in 1914 and 1916, there was no epidemic of influenza amongst the troops, and yet the organism recovered most frequently by several independent observers from the characteristic sputum was the so-called influenza bacillus, the bacillus of Pfeiffer.

This peculiar form of purulent bronchitis has been seen as a complication of the undoubted influenza epidemics of 1918 and 1919, but this fact is probably of little importance, as compared with the undoubted absence of true influenza in epidemic form at times when purulent bronchitis was prevalent. A few cases of purulent bronchitis of the severe type have occurred at all times during the campaign, and this malady when it occurs in association with influenza should be regarded as a true complication, but it is not restricted in its incidence to influenza cases.

(2) *Pneumonia*. Several varieties of true pneumonia causing areas of consolidation of very varying size and following in different cases different courses, are, as is well known, common lesions in fatal cases of influenza. The areas of consolidation vary enormously in their size and in their naked-eye appearance. Thus in some cases they are so small and so widely distributed as to suggest at first the presence of miliary tubercles. In others, they are so large, and neighbouring ones have coalesced to such a degree, that a superficial resemblance to the red or grey hepatization of lobar pneumonia may be produced. This is especially the case when very large portions of a lobe of the lung are involved. True lobar pneumonia as a complication of influenza would seem to be rare. In most, if not in all, cases of influenza complicated with lobular pneumonia, the lung is deeply congested and small haemorrhages of varying size in the substance of the lung are common. Further, the lung section, as seen at autopsy, is unduly wet, and much fluid can be extruded by pressure both from the lung substance and from the cut bronchi. The lung, if held up, drips much fluid, often blood-stained, but the naked-eye appearance is quite different to that of ordinary oedema of the lung, inasmuch as in influenza the lung is deeply congested, and very airless even in the non-pneumonic areas.

(3) *Haemorrhagic oedema of the lung*. The most striking pulmonary lesion of influenza, however, is not the lobular pneumonia nor the bronchitis, important as these are; it is rather the intensely congested, haemorrhagic, wet, and sodden appearance of large areas of the lung substance. It is true, as just stated, that this condition is often found in association with definite pneumonic lesions, but large areas of the lung, even the greater part of one or both lower lobes, may present this deeply congested, wet, and sodden appearance, without any actual consolidation being present. Such a lung presents on section a uniform red or dark red appearance; the cut surface may be somewhat glazed or gelatinous looking, or simply unduly but uniformly moist. The cut surface exudes, often without pressure, a quantity of thin blood-stained fluid, and the quantity of this is much increased by pressure. The bronchial tubes may, and usually do, contain large quantities of similar frothy fluid. The portions of the lung involved are relatively airless, although by no means completely collapsed, and numerous haemorrhages of varying sizes, but often small, may be seen scattered over the surface. This lesion is especially well seen in the formidable cases that die quite early in the disease, but it may also be seen in certain other cases where, after an illness of some days of an apparently mild nature, severe symptoms develop suddenly, and death occurs in a few hours. In these cases the expectoration of an abundant blood-stained sputum, may be a striking clinical feature, but this is not such a constant phenomenon as is the presence of cyanosis.

This condition presents a superficial resemblance to oedema of the lung, but it is really quite different both clinically and anatomically. The essential clinical difference lies in the absence of the urgent dyspnoea that is so marked in oedema of the lung whatever its origin. Thus dyspnoea is marked in oedema of the lung arising in such widely different conditions as the uraemia of chronic renal disease



on the one hand, or chlorine gas poisoning on the other. In these influenza cases, the rate of respiration is not necessarily greatly increased, and the absence of any urgent symptoms, other than cyanosis and perhaps a slow pulse, may cause the extreme gravity of the case to be overlooked.

Anatomically the condition differs from true oedema in that uniform congestion is so marked a feature, and the lung is relatively airless. Further, the exuded fluid is different, in that it is so generally blood-stained. It is probable that this wet, sodden, extremely congested lung, with its scattered haemorrhages of varying size, is to be regarded as the essential pulmonary lesion of severe influenza. Frequently pneumonic lesions are superadded, but they are essentially complications.

4. *Pleural effusion.* Pleural effusion is not an uncommon complication of influenza. Such cases often present a very definite clinical picture, in that, although the effusion is usually moderate in amount, the pyrexia is apt to be high and the patient often profoundly ill. Unless carefully examined, the signs present in the chest are liable to be interpreted as due to pneumonic consolidation, whereas in reality an effusion is present. The fluid when removed by exploratory puncture or by aspiration may present a remarkable opalescent appearance, and, as recorded by Capt. Wilson in the bacteriological section of this communication, the filter-passing organism of influenza is present in such fluid in pure culture and in enormous numbers. In other cases the pleural fluid may be straw-coloured, and so somewhat resembles to the eye that seen in cases of acute pleurisy with effusion due to infection with the bacillus of tubercle. In a certain proportion of cases the fluid is turbid or even frankly purulent, and although the influenza organism is present in these purulent fluids, other secondarily infecting organisms are also usually associated with it. The main point of interest lies in the fact that the filter-passing virus of influenza may be found in, and be responsible for, a pleural effusion presenting clinically some resemblance to the well-known form associated with tuberculous infection.

In some cases the effusion, although not very large in amount, recurs after paracentesis, but usually only to a small extent, and it is exceptional for paracentesis to be required more than twice. In others the effusion is bilateral, but here also it is usual for the effusions to be of moderate size.

When the presence of an effusion is associated with pneumonia either on the same or on the opposite side, the outlook is grave, but the great majority of the cases of influenzal pleural effusion recover, although progress is often slow and the pyrexia may persist for several weeks, thus again simulating tuberculous pleurisies.

*Clinical.* The outstanding feature of the second and third epidemics of influenza has been the great frequency with which the lungs have been affected and the rarity of the involvement of either the nervous system or the gastrointestinal tract. Very few cases of influenzal meningitis or even of meningismus have been seen, but the filter-passing virus of influenza has been recovered



from the cerebro-spinal fluid in the only case of meningitis that came under observation.

A few cases of jaundice of moderate severity have been observed coming on a few days after an attack of influenza. Here also the filter-passing organism has been recovered from the blood during the initial and early febrile stage of the jaundice. This observation is of interest in view of the marked hepatic lesions observed in the experimental animals inoculated with the culture of the organism obtained from uncomplicated cases of influenza. Further, the presence of the organism in large numbers in the bile of the experimental animals, and the successful use of the bile of these animals as a means of inoculation in passage experiments, are facts of interest in relation to this occurrence of jaundice as a complication in influenza in man.

Nephritis, usually of a moderate degree of severity and only of transitory duration, but occasionally serious, has been observed more frequently as a complication in cases presenting at first only pulmonary lesions. The filter-passing organism has been recovered from the urine of such cases, but not from the urine of influenza cases where no nephritis was present.

In a considerable proportion of the more serious cases of influenza there is a marked tendency to haemorrhage, and two forms at least of this are seen. In one the haemorrhage occurs from the respiratory tract, and in the other it takes place in the voluntary muscles, and more especially the rectus abdominis. In the former the sputum, which may either be copious and watery, or scanty and glutinous, contains varying quantities of bright red blood. This sputum, totally different in appearance from the well-known rusty sputum of pneumonia, is very characteristic of some of the most severe and fulminating cases of influenza, where the lung lesion is extensive and of the sodden, wet, and haemorrhagic type described above. The sputum owes its characteristic appearance to its glutinous consistence together with the admixture of bright blood. The patient may experience considerable difficulty in expectoration owing to the stringy and glutinous character of the phlegm. Such a sputum would seem to be a very characteristic feature of the more severe forms of the disease. The other type of sputum, watery, viscid, and blood-stained, is also important and may be dangerous, not so much from any difficulty in its expectoration, but rather from its quantity. A similar fluid is often found in abundance in the bronchial tubes on post-mortem examination.

*Physical signs.* These necessarily vary according to the severity of the case and the presence of complications, and do not call for detailed notice here. It is, however, of some importance to recognize, that in severe influenza a casual examination of the chest may seem to show that no lung lesion is present, whereas a more careful examination will reveal certain signs not only characteristic but also of importance, since they may be the only signs indicative of the gravity of the case. Coarse signs, such as marked dullness on percussion, tubular breathing, adventitious sounds, may all be absent in the early stages of the infection. On careful examination, however, even within less than

twenty-four hours of the onset of the disease, an area, often large and perhaps even involving an entire lower lobe of the lung, may be found where the air entry is deficient, as shown by the weakness of the breath sounds. At first nothing more than this can, in many cases, be detected, but later, and sometimes still quite early in the course of the disease, the percussion note becomes decidedly impaired although not dull, and a few fine râles may be heard on auscultation. The important physical sign is, however, the weakness of the breath sounds over a definite area, large or small, as the case may be. These signs, of course, present some analogy to those found at the onset of pneumonia, but in influenza such signs are by no means invariably the initial signs of pneumonic consolidation, although sometimes this is the case. There is every reason to believe that these apparently unimportant signs are really the physical signs of the sodden lung described above. Not uncommonly these signs are associated with the expectoration of the sanguinolent sputum mentioned above, but they may exist in a well-marked form when no expectoration is present, and this is equally true of the lung lesion, as this is not always accompanied by the expectoration of this sputum. Cyanosis, however, is more constantly present in such cases when the area of the lung involved is large and when the patient is gravely ill. It is remarkable how few symptoms such patients present; the rate of respiration may not be much increased, and it is often well under thirty per minute, and the pulse-rate may also be slow.

*Conclusions.* The results recorded in the present communication derive their main significance from the correlation of the bacteriological results with those obtained from suitable experimental work on animals. The detection in the human subject and the successful cultivation of an organism, even from a large series of carefully controlled cases, cannot be regarded as affording any real proof that the organism in question is the cause of the malady. When, however, the pure culture of the organism in question reproduces in the experimental animal lesions of a character similar to those found in the disease in man, and further the organism is again found in such animals and can be recovered from its tissues, the proof becomes much stronger and such evidence is usually accepted as proving that the organism in question is the actual cause of the disease. The facts detailed in this paper afford such evidence in the case of the filter-passing virus of influenza, as has already been stated in the preliminary report<sup>1</sup> presented to the Director-General of Medical Services, British Armies in France. The characteristic lesions of influenza in man have been reproduced in the experimental animal, e.g. the peculiar lung lesion, the fatty change in the heart and liver, the nephritis, the cerebral lesions, and the peculiar haemorrhagic lesion in the voluntary and cardiac muscles.

The experimental results, however, go much further than this, as they reveal the remarkable vascular lesions produced in the small arterioles by the virus of influenza. These results, therefore, support the view that influenza

<sup>1</sup> 'Preliminary Report on the Presence of a "Filter-Passing" Virus in Certain Diseases.' *British Medical Journal*, Feb. 1, 1919.

is to be regarded, not as a local disease of the respiratory tract, but as a general infection of the blood-stream with the localization of marked lesions of a special character in the smaller blood-vessels. The vessels of the lungs suffer to a very special degree, and the peculiar sodden haemorrhagic lung is the result. Doubtless such a damaged tissue is prone to suffer from secondary infections, hence the prominence of the pulmonary lesions in this disease. Other organs and tissues are, however, affected, e. g. heart, kidney, voluntary muscles, brain, &c. Other work has been done on the same lines with the filter-passing viruses isolated from other diseases, e. g. polyneuritis, encephalitis, nephritis, and the results obtained with these organisms have served to control the influenza results. All these organisms present certain points of resemblance to one another in their morphology, in their cultural reactions, and also to some extent in their actions on living tissues as pathogenic agents. There are, however, individual differences in their actions, and it is in the light of these facts that we regard the lesions produced by the filter-passing virus of influenza as described in the body of this paper as specific and characteristic of its activity.

#### THE EXPERIMENTAL REPRODUCTION OF THE DISEASE BY MEANS OF THE INOCULATION OF THE ISOLATED VIRUS, TOGETHER WITH A DESCRIPTION OF THE NATURE OF THE LESIONS

By E. F. BASHFORD

The purpose of this paper is to supply experimental evidence that an organism, isolated by Capt. J. A. Wilson, R.A.M.C. (T.C.), from cases of influenza in man, fulfils the requirements which are necessary before its claim to be the cause of the disease may be regarded as established. The nature of the pathological processes induced experimentally will be described, and the new light they throw on the grave course of the disease in man indicated. It will also be shown, on the one hand, that the virulence of the organism can be enhanced by passage, and, on the other hand, that the course of the experimental disease has been modified favourably in preliminary experiments, in so far as the lesions of the lungs are concerned. Complications by the addition of other infective processes are not considered.

Since 1893 (1) the bacillus of R. Pfeiffer has been known as the *Bacillus influenzae*, although adequate confirmation has been lacking. Competent observers doubt or deny that any epidemic similar to the one through which we are now passing has occurred since. This organism was held to be the cause of 'epidemic grippé' because of its almost constant presence, and this inadequate argument is still adduced to-day. It was present not only in the abundant expectoration, and the layer of pus in the higher respiratory passages,

where it is described as often present in pure culture; but also, in severe infections it was described as finding its way downwards into the areolar tissue of the lung and producing there nodules of broncho-pneumonia, sometimes of large dimensions, numbers of the bacilli being often found contained in polymorphonuclear leucocytes in the alveoli. The chain of evidence has never been completed by experimental proofs. It was admitted that for animals it was not pathogenic as a rule; cultures injected intravenously in large doses into rabbits were only occasionally fatal, and, if not, produced merely toxic effects. The intratracheal injection of cultures in monkeys produced catarrh of the respiratory passages. Other consequences observed only in man, e.g. acute meningitis, petechial haemorrhages, and venous thrombosis in the brain, and yet other remote symptoms such as neuritis, together with the great constitutional disturbance, were ascribed to the potent toxic action exerted from the pulmonary foci. In short, the cultural bacteriology of the organism was well defined, its pathogenesis unproved, and its morphology in the tissues and the inflammatory exudates vague. In extenuation of the many exceptions and deviations from the generally accepted canons for establishing aetiology, it was claimed that the difficulties overcome in discovering this organism as the cause of influenza were largely due to its small size, the difficulty of distinguishing it from certain cocci, and the necessity for devising a special culture medium. Truly, a confession of inability to fulfil Koch's law. Nevertheless the pathogenesis of the disease as conceived since 1893 has remained the same. The *B. Pfeiffer* was inhaled from the spray distributed by some other individual, and thereby a catarrhal inflammation was set up, which extended downwards from the upper air passages to the lung, and in the most severe cases came to invade even the areolar tissues, producing fatal effects, either by itself, or because of the superposition of some other infection (2). The idea that the essential process might be primarily a constitutional infection with specific incidence on certain tissues was not generally accepted, many writers regarding the disease as primarily an infection of the upper respiratory tract.

The descriptions given in the following pages demonstrate that, having found entrance to the body, the organism is present in the blood for a long period, and the effects of its presence there are exercised primarily and most disastrously on the circulatory system with grave secondary consequences.

*Results of inoculating Sputum Filtrate and of the Isolated Virus.*

The total number of primary inoculations made between June 24, 1918, and February 9, 1919, was 41.

Only very few monkeys (*M. rhesus*) were available, and rabbits and guinea-pigs were so difficult to obtain, and when found so costly and so sickly, that reliance had to be placed almost solely on those bred in the laboratory. Therefore long series of experiments have been impossible, and those made are

not as numerous as might be desirable; but every care has been taken to keep the animals in good health, and by accurate observation to make the results reliable. No epidemic occurred among the laboratory stock. In the course of the investigations there was only one death, that of a rabbit, possibly from intercurrent disease.

*Inoculation of filtrate of sputum.* The experimental observations on influenza were carried out concomitantly with those already recorded in detail for polyneuritis, and more briefly for encephalitis, nephritis, and other diseases. The first experiment bearing on influenza was made on June 27, 1918, and the last of the preliminary series on polyneuritis on July 11, 1918.

*Experiment 1. Monkey 10. June 27, 1918.* The filtrate of the pooled emulsion in glycerin of the naso-pharyngeal mucus of ten patients suffering from influenza was received from Capt. J. A. Wilson, and a drop inoculated subdurally into a male *Macacus rhesus*. Beyond holding its hands on the head, and being generally sluggish and out of sorts, there was little to attract attention during the following days; but on July 1 the animal was obviously ill, and running at the nose. There were sudden contractions of the muscles of the limbs, especially of the shoulder-girdles, and the head was suddenly retracted. By July 3 the monkey was really better; but slight jerks still occurred, and on the fifth the animal was apparently quite well. If a positive result is claimed, then only a slight or attenuated form of the disease appeared to have been produced. The experimental observations were interrupted, and ultimately brought to a standstill for more than three months owing to the demolition of the laboratory and its subsequent reconstruction, work being resumed in October.

*Inoculation of cultures of the isolated virus.* The above was the only experiment in which the method already described by Nicolle and Lebailly (3), and Major Gibson, Major Bowman, and Capt. Connor (4), was employed alone. All subsequent experiments were made with the subcultures prepared by Capt. J. A. Wilson from the blood, the sputum, and the pleural fluid respectively of influenza patients. Altogether six subcultures were tested, five of the second, and one of the third generation, there being no noticeable difference in the effects produced; in particular there was no loss of virulence on subculture.

Owing to their historical interest the notes made by Corp. T. C. Reynolds, R.A.M.C., of the first experiment with the isolated virus are transcribed below:

*Experiment 2. Monkey D.*

- 11.11.18. About 2 c.c. of ten days' growth of influenza culture from Capt. J. A. Wilson, inoculated intravenously right femoral.  
14.11.18. Conjunctiva suffused, shivers in sunshine, eats little.  
15.11.18. Appears better, eats better, conjunctivitis has gone, runs at nose.  
18.11.18. Has recovered from toxic action (?).



- 27.11.18. Quite well since previous date.  
30.11.18. 0.25 c.c. culture sputum filtrate intravenously right femoral.  
1.12.18. Quite well.  
3.12.18. „  
5.12.18. Quiet and pale, sick looking.  
7.12.18. Better and brisker.

(See further under effect of reinoculation.)

Two mild attacks of illness followed the inoculations, the first being more marked than the second. This difference was not due solely to the smaller dose of the second inoculation, because of the more severe effects produced in another monkey (Monkey M) which received the same dose of the same culture in the same way (Experiment 4).

Intravenous inoculation had been selected in the first place because of the recovery of the organism from the blood in man, but it was evident early that the disease, if it was reproduced by intravenous inoculation, was manifested either in an attenuated or a modified form. Perhaps, without the experience gained during the close observation of monkeys after their inoculation with emulsion of tissue and cultures from cases of polyneuritis, the significance of the symptoms following similar inoculations in the case of influenza might have been misunderstood, or missed altogether. Hence the experiments were extended to rabbits and guinea-pigs, the methods of inoculation varied, animals killed in order to study the lesions more closely, especially in order to observe the effects of 'passage', and the results of attempts to recover the organism.

*Experiment 3.* On Nov. 19, 1918, a monkey and a rabbit were inoculated subdurally with a six days' subculture, and a guinea-pig intravenously, the mesenteric vein being selected because the marked involvement of the liver in the human being suggested a direct attack by this channel.

*Monkey F.*

- 19.11.18. Inoculated subdurally with a six days' growth influenza subculture.  
23.11.18. Eyes injected slightly.  
25.11.18. Eyes injected heavily.  
27.11.18. Not looking so well generally. Eyes still the same.  
29.11.18. Improving.  
3.12.18. Practically well.  
8.12.18. Quite well.  
21.1.19. „  
7.2.19. „

*Rabbit F.*

- 19.11.18. Inoculated subdurally with six days' growth influenza subculture.  
27.11.18. Quite well since previous date.



29.11.18. Quite well.  
 3.12.18.        "  
 8.12.18.        "  
 21.1.19.        "  
 7.2.19.        "  
 10.2.19. Killed.

*Guinea-pig F.*

.11.18. Inoculated intravenously into mesenteric vein with six days' growth influenza subculture.  
 24.11.18. Temp. 103.2°. Ill.  
 25.11.18.   " 105.0°   "  
 26.11.18.   " 104.0°   "  
 27.11.18.   " 103.4°   "  
 28.11.18.   " 104.2°   "  
 29.11.18.   " 104.2° Moribund.  
 29.11.18. 3 p.m. Killed. Wound quite cleanly healed.

Subdural inoculation produced very similar and quite as good results in the monkey as intravenous injection notwithstanding the smallness of the dose. There was no noticeable effect in the rabbit during life. Intravenous injection, via the mesenteric vein, in the guinea-pig, produced the most marked effect on the temperature and general health yet obtained. The animal was killed when it appeared to be moribund. The liver was pale and discoloured, with what looked like haemorrhages, the naked-eye coloration simulating that of acute yellow atrophy. The lungs were discoloured with large dark red or purple blotches, and the kidneys were injected. There was now reasonable evidence that the disease had really been reproduced in a still more attenuated form in the case of the earlier experiments. Moreover, consideration of the age or days of growth of the cultures showed that it had been of importance in the effects produced in monkeys; ten days' produced less result than six days' growth, and, as the following experiments show, also less than a four days' growth.

*Comparison between Inoculation of Sputum Filtrate and Isolated Virus.*

*Experiment 4.* After positive results were obtained by the inoculation of the isolated virus in monkeys and guinea-pigs it seemed advisable to institute a comparison between filtrate and the culture obtained from it. Therefore, on November 30, 1918, two monkeys were inoculated intravenously, via the femoral vein, with filtrate of sputum preserved in glycerin and a subculture of four days' growth obtained from the same sputum. At the same time two guinea-pigs were inoculated subdurally. It seemed desirable to make the comparison by more than one method of inoculation, and on the animal that had proved most susceptible. The essential notes are transcribed below:

*Monkey L.*

- 30.11.18. Inoculation of 0.25 c.c. of filtrate of influenza sputum.  
 1.12.18. Quite well.  
 3.12.18.       "       "  
 5.12.18.       "       "  
 6.12.18.       "       "  
 8.12.18.       "       "  
 11.12.18.       "       "  
 13.12.18.       "       "  
 7.1.19. Runs at nose and eyes.  
 21.1.19. Quite well.

*Monkey M.*

- 30.11.18. Inoculation of 0.25 c.c. sub-culture of influenza virus from same sputum as monkey L, four days' growth.  
 1.12.18. Quite well.  
 3.12.18. Runs at nose.  
 5.12.18.       "       "  
 6.12.18. Marked running at nose.  
 8.12.18.       "       "  
 11.12.18. Quite well.

Whereas the monkey inoculated with the culture developed symptoms within five days of inoculation, that which received filtrate of sputum did not do so, nor was there anything to attract attention till more than a month later.

*Pig L.*

- 30.11.18. A drop of filtrate of influenza sputum, inoculated subdurally.  
 1.12.18. ? ill. Temp. 101.0°.  
 2.12.18.       "       101.4°.  
 3.12.18. Hair on end. Temp. 101.8°.  
 4.12.18.       "       "       "       101.4°.  
 5.12.18.       "       "       "       101.6°.  
 7.12.18. Killed because getting better.  
 Lungs, numerous minutered spots. Liver, nothing to naked eye, but pale, large. Kidney, injected. Urine from bladder injected subdurally into Pig L 2.

*Pig M.*

- 30.11.18. A drop of second-generation culture of influenza virus, four days' growth. Inoculation subdurally.  
 1.12.18. Ill. Temp. 103.2°.  
 2.12.18.       "       100.8°.  
 3.12.18. Hair on end. Temp. 101.8°.  
 4.12.18.       "       "       "       100.8°.  
 5.12.18.       "       "       "       100.4°.  
 7.12.18. Killed. Liver pale and enlarged with minute red spots. Lungs, usual findings. Urine into Pig M 2. Gall into Pig M 3.

The difference between the two pigs was less than between the two monkeys; it was, however, more marked than might be inferred from the notes. The filtrate of sputum hardly disturbed the normal temperature curve, which varied around 101.6°. In the case of the culture the temperature remained below normal, after a slight preliminary rise, a sign of bad health in guinea-pigs. In the case of the culture the lesions after death were also more pronounced, so that, e.g., the lungs of Pig M are depicted in Fig. C2 as typical moderate lesions, whereas those of Pig L have only been examined microscopically recently, while completing the histological survey of the material

accumulated. Moreover, four out of the five attempts to recover the organism from the organs of Pig M were successful, and one doubtful, whereas for Pig L two out of four were negative.

For polyneuritis a similar and better result has already been recorded for culture, as contrasted with the emulsion of the spinal cord preserved in glycerin from which the culture was prepared. Whether this better result is due to the absence in the cultures of reaction products or of toxins contained in the tissues and fluids of man, and perhaps inducing immunizing reactions in animals, or is in the main a question of dosage remains a matter for further inquiry. It is significant that no such difficulty exists when the transference is effected from one animal to another of the same species in the case of polyneuritis, encephalitis, influenza, and trench nephritis. At any rate it appears to be an essential factor in the success which has attended the experimental reproduction of these diseases, that an actual culture has been interposed in the passage from man to animals, instead of merely transferring human body fluids, excretions, or tissues directly to animals. Thereafter, passage by tissue, blood, bile, or urine has been easy. This point of view may justify a still wider outlook, and may permit of a perfectly open mind as to the aetiology or nature of a larger number of diseases, some of which are generally regarded as 'congenital' or otherwise beyond the scope of the combined skill of the physician and the resources of the laboratory, and, yet others, such as measles or scarlet fever, so notoriously infective that their danger to child life is common knowledge even among the less well informed.

#### *Inoculation of Mixture of Influenza and Nephritis.*

The occurrence of acute nephritis in some cases of influenza suggested mixing the two organisms to ascertain the effects of possible symbiosis. Such an experiment was also required in connexion with attempts to recover and identify the organisms. This was effected, but a day later, subdurally in a monkey, a rabbit, and a guinea-pig, with the same subculture of influenza as employed in Experiment 4.

##### *Experiment 5. Monkey G (female).*

- 20.11.18. Inoculated subdurally with a mixture of influenza and nephritis subcultures.
- 22.11.18. Apparently bad headache.
- 24.11.18. Breathes audibly. Runs at nose.
- 27.11.18.       "       "       "
- 5.12.18. Has been running at nose for past week.
- 7.12.18. Sneezing and still running at nose.
- 8.12.18. Runs at nose.
- 21.1.19. Occasionally running at nose.
- 7.2.19. Well.

*Rabbit G.*

- 20.11.18. Inoculated subdurally with a mixture of influenza and nephritis.  
24.11.18. Temp. 103.2°.  
29.11.18. Quite well.  
3.12.18.       "  
5.12.18.       "  
8.12.18.       "  
19.1.19. Died. Evidence of diarrhoea, intestines inflamed with hæmorrhagic patches. Kidney injected cortex especially at boundary layer. Lungs, liver, doubtful.

*Guinea-pig G.*

- 20.11.18. Inoculated subdurally with a mixture of influenza and nephritis.  
22.11.18. Pig out of condition. Hair bristles, moves slowly, trembles.  
24.11.18. Eyes run. Audible râles, respiration laboured. Temp. 105.4°.  
Killed 11 a.m. because apparently moribund. Marked lesions of lungs, liver, and kidney.

The rabbit again showed no effects during life and may have died of intercurrent disease. Both the monkey and the guinea-pig exhibited very marked evidence of respiratory trouble; the temperature of the pig rose to 105.4°, the highest yet seen. In the monkey there appeared to be also some effects on the meninges. A fairly good conception of the symptoms and lesions had now been obtained, as well as of the relative importance of the age of cultures, influence of dose, and method of inoculation, so that with one exception further protocols may be dispensed with.

*Summary of the Effects produced by Primary Inoculations.*

Positive results are claimed for nineteen out of twenty experiments, i.e. with the one doubtful exception of a rabbit. This conclusion is based on the evidence during life or after death respectively, or on the combined evidence of both. The protocol of the most severe and typical form of the disease induced in the monkey (N) is given below under complications by nephritis (Experiment 6).

*Symptoms produced.* The symptoms produced were similar irrespective of the method of inoculation and material used. Of the monkeys, only the first exhibited marked muscular contractions which may have been meningeal in origin. All the others showed injection of the conjunctiva on second, third, or fourth day, together with running at the nose and eyes. About the fourth day there was shivering and 'staring' of the hair. About the same time there was sneezing, and in the most marked cases there was audible breathing, as if the nostrils were occluded, but even audible râles accompanied by a distinct cough have been noted. All the monkeys were little interested in food proffered, and appeared to have poor appetites.

The temperatures were not recorded owing to the vagaries exhibited in untamed animals. None of the monkeys appeared seriously ill, none died, and one was killed after a primary inoculation, being seriously ill with pulmonary symptoms from twenty-four hours onwards, and from the fifth day also with nephritis. The post-mortem lesions in this monkey were typical, both naked eye and microscopically.

In guinea-pigs all the above symptoms were more marked. The animals rubbed their noses with their forepaws as if trying to remove an obstruction. Running at eyes and nose were constant, sneezing and hair 'staring' also. Audible breathing, râles, and laboured breathing were noted in severe cases.

Of thirteen pigs, one died and seven were killed, most of which were moribund, seven to fifteen days after inoculation. One of these, Pig L, inoculated with sputum filtrate, was killed when recovering. Five were reinoculated, of which two still survive. This is, however, no criterion of the influence exerted by a primary inoculation on succeeding ones, as will subsequently be stated. The increased severity of the symptoms in guinea-pigs as compared with monkeys is partly referable to the relatively much larger dose inoculated, but a greater susceptibility cannot be excluded.

The temperatures of the guinea-pigs were taken *per rectum* morning and evening, and charts kept in order to ensure a careful supervision of the animals, as well as to elicit any useful information from the curves. The temperature of other control guinea-pigs kept in the laboratory ran uniformly between 101° and 102° Fahr., averaging about 101.6°. Subcutaneous inoculation had little or no effect on the temperature. Subdural inoculation had more effect, usually causing the temperature to rise within twenty-four hours, and in one case to 105.4°. A sudden preliminary fall occurred in some cases even below 98°. Such pigs were obviously very ill. The rabbits did not attract attention during life, but when killed showed pulmonary and renal lesions comparable with those found in the guinea-pigs at a corresponding interval after inoculation. In view of the success attending the inoculation of pigs, rabbits could not be spared, being ear-marked for the investigation of other diseases for which they were indispensable.

*The naked-eye lesions observed after primary inoculations.* All the animals that died or were killed showed obvious lesions of the lungs, liver, kidneys, and heart. In one case there was obvious naked-eye haemorrhage in the anterior abdominal wall, and an excess of fluid on exposing the brain was suspected. The thoracic organs were removed intact after ligaturing the trachea, &c., in the neck. In the monkey and one guinea-pig there was some fluid in the thoracic cavity, and in one pig slight fresh fibrinous adhesions towards the base of the left lung. The trachea of the pig that died contained blood-stained mucus. In severe cases the normal pale pink coloration of the lungs gave place to a uniform dark purple-red colour, as if there was complete consolidation of both lungs, except for irregular extensive areas or spots of emphysema. Outwardly such lungs resembled the consolidation of red hepatization of lobar pneumonia.

On section, however, abundant froth was extruded from the uniform red mass. In less severe cases the distribution was like that of broncho-pneumonia. Such lungs showed rounded spots or blotches of dark red superimposed on the more normal background. The dark areas had the appearance of being solid even after embedding in paraffin, but microscopical examination showed that this appearance was merely due to the way in which they were looked at by reflected or transmitted light. They really radiated out diffusely into the areolar tissue from the bronchioles. Patches of emphysema occurred, most frequently round the margins, but also over the surface.

The liver was enlarged and pale, or pale with minute red spots. In one case (Pig F), ten days after injection via the mesenteric vein, the mottling of the liver, combined with extensive if somewhat diffuse red discolorations, closely resembled the early stages of acute yellow atrophy. The lobular arrangement was exaggerated to the naked eye. The fissuring was exaggerated and the substance friable to the fingers. The gall-bladder was usually distended, containing abnormally pale yet greenish bile; once the fluid was colourless, containing much flocculent mucus, owing to obstruction of the cystic duct.

The upper portion of the small intestine showed evidence of acute inflammation in several cases. In the two pigs that died (one after reinoculation) there were haemorrhages into the mucous membrane of the large intestine, which was greatly distended with gas. In one of these pigs (N 3) the stomach was empty.

The kidneys appeared normal, or to the unaided eye resemble in miniature the kidneys typical of the nephritis of scarlet fever.

The heart was enlarged, the right ventricle especially appearing distended but flabby, and there were obvious and numerous subpericardial haemorrhages up to the size of a pinhead. In one case there was a fair amount of pericardial fluid.

Little was noted naked eye in the brain, except in one case where there seemed to be an excess of fluid. There was nothing unusual in the subcutaneous tissue, or in the suprarenals, beyond that they seemed large. The spleen varied, but on the whole seemed uniformly too large. The nasal mucous membrane appeared healthy. The voluntary muscles were examined for visible haemorrhage, but in only one case was this easily observed in the anterior abdominal wall.

Therefore the naked-eye lesions closely reproduced those seen in man, especially as regards the lungs, heart, and liver, and also in the case of the kidneys, although in man they have attracted less attention than they merit. The detailed examination of the lesions is dealt with separately later on.

*Complications by nephritis.* It was noted early that after death there was microscopical evidence of acute nephritis supervening in guinea-pigs. As the urine of several monkeys had been under examination in the concomitant experiments on trench nephritis, a healthy male monkey was inoculated on December 4, 1918, with 2 c.c. of influenza subculture of six days' growth, into the mesenteric vein. The protocol is transcribed below :



*Experiment 6. Monkey N.*

- 4.12.18. Inoculated.  
5.12.18. Ill, hair on end, holding head.  
6.12.18. No albumin in urine, ill, hair 'staring', nose running, holding head.  
7.12.18. No albumin in urine.  
8.12.18. " "  
9.12.18. Traces of albumin, running at nose, monkey frequently coughs.  
10.12.18. Albumin present, running at nose, monkey frequently coughs, and is ill. There were red blood corpuscles, granular and epithelial casts, four found in a field of the centrifugalized urine. Killed 3 p.m. Operation clean. Fluid in chest; slight adhesion of pleura. Liver pale, enlarged. Large pale kidneys, cortex thickened as compared with Monkey O (inoculated with nephritis culture at same time and in same way).

The monkey developed marked respiratory symptoms within twenty-four hours, and by the fifth day albumin began to appear in the urine. Of six monkeys this was the only one in which clinical evidence of nephritis was deliberately sought for and confirmed microscopically. Of the other five, two with much milder respiratory symptoms were under close observation; and it is unlikely that it was missed if it occurred in the same degree. The sixth monkey was a female and therefore unsuited for clinical observation of the urine. In guinea-pigs the examination of the urine is unsatisfactory, but on microscopical examination nephritis was present in five out of nine in varying degree.

From a survey of the foregoing observations the conclusion is warranted that the incidence of the disease after inoculation of pure cultures fell with such uniform severity on the respiratory passages, lungs, and kidneys, as to reproduce, although sometimes only in a mild form, striking clinical features of influenza in man, after an incubation period of from one to three or four days. In the monkey no primary inoculation advanced to a fatal issue, although Monkey N developed a severe form of the disease in all its typical features and was killed for histological material and other purposes. Only one guinea-pig was actually allowed to die after a primary inoculation, and eight, being more or less moribund, with subnormal temperatures and complete loss of appetite, were killed, i.e. not more than about 60 per cent., and probably much less may have been expected to die ultimately.

*Influence of the age of the cultures.* The age of the cultures varied from four to ten days' growth. There was a distinct evidence that, irrespective of the methods of inoculation, the younger cultures produced the more marked effects. The incubation period was also shortened for four days' growth to twenty-four hours, as contrasted with three days for a nine days' growth. An incubation

period of twenty-four hours was obtained for sputum filtrate, primary cultures, and for subcultures. There is thus evidence of variability in virulence.

*Influence of the dose.* The dose was important, influencing the severity of the effects rather than the rapidity of onset in the case of intravenous inoculation, the incubation period being again shortened to twenty-four hours by the injection of 1 c.c. of six days' growth. No noticeable effect followed varying the size of the doses given by subcutaneous injection, and it is not possible to determine what the slight variations between individual subdural inoculations may have been apart from the age of the several cultures.

*Influence of method of inoculation.* Little or no evident effect followed the subcutaneous injection of as much as 1.5 c.c. The most constant and rapid and severe effects were obtained by subdural inoculation both in monkeys and guinea-pigs. The incubation period was only twenty-four hours in three out of four pigs, with growths of four and five days as contrasted with three days for a nine-days' growth. Intravenous injection, via the jugular vein or femoral vein, while yielding positive results fell behind subdural injection.

It is apparent that the gravity of the results of primary inoculations is influenced by a variety of factors, the relative importance of which it is not possible to appraise accurately in the present state of our knowledge. Moreover the manner of onset of the symptoms within twenty-four hours suggests that they may be further complicated by the action of a toxin which, as described later, seems to exercise very rapid effects on vascular endothelium. These effects were studied in animals after a subdural inoculation where errors are excluded which might arise from infarction, thrombosis, and other consequences of direct injury to vessels, and especially to vascular endothelium, e.g. in the heart, lungs, liver, kidneys, brain, and muscles.

#### *Recovery of Organism from Inoculated Animals.*

Tissues, blood, urine, and bile of animals dying or killed were placed in 50 per cent. sterile glycerin so far as they could be spared from other purposes. Specimens from certain typical experiments were handed to Capt. J. A. Wilson, after being kept in glycerin from a few days to several weeks. The organism was successfully recovered in every case, including a passage experiment (Pig M 3) made with bile by the subdural route. The prolonged stay of the organism in the blood is remarkable, and in striking contrast to the mildness of the symptoms. In this connexion Pig L, inoculated with sputum filtrate, is noticeable. During life there were no symptoms; at death no naked-eye lesions; microscopically there was nothing in the liver, not even a noticeable presence of round cells in the portal tracts; in the kidney there was congestion of some of the glomeruli with some exudate in the capsule, but only revealed after prolonged searching. In the lungs it is possible there was a uniform increase in the cellularity of the trabeculae, and therefore of their

thickness; here and there slight congestion was evident. The attempts to effect passage by the subdural inoculation of the urine of this pig, and also with that of Pig M, were negative, and yet the organism was recovered from the kidneys of both on the seventh day.

The organism has been recovered from the blood, liver, lung, kidney, urine, gland, and from bile. The organs contained blood, the animals not having been perfused. The important fact is that the organism is not localized solely in the organs of respiration, although remaining there for as long as eighteen days after inoculation. Apparently it remains in the lung after it has passed from the blood and the liver, so that the mere presence of blood in the organs would seem to afford an inadequate explanation. The presence of the organism in the liver after subdural inoculation appears in marked contrast to its absence in that organ after injection via the mesenteric vein. The organism is, however, readily found in the bile stained by Leishman, Giemsa, or Jensen's modification of Gram staining. It has been found in the bile of three of the four animals so examined. Its presence receives confirmation from the transmission of the disease by passage from animal to animal by inoculation of bile, and the recovery of the organism from an animal so inoculated. The organism has not yet been detected by direct examination of the urine. Two passage experiments were made by the subdural inoculation of urine of Pigs L and M respectively; both were negative, yet the organism was recovered, and in culture from the urine of three monkeys after primary inoculation, and that of one pig in a passage experiment made subdurally with bile (Pig M 3).

#### *Passage Experiments.*

These were performed on guinea-pigs by the transference of full blood, citrated blood, bile, urine, and emulsion of the lung, two to ten days after the primary inoculation. The virulence of the organism was found to be enhanced in the case of blood, bile, and emulsion of lung; but the results of the transference of urine were negative. Blood produced severe, practically fatal, symptoms within two days. Emulsion of lung produced such marked illness that the pig was killed on the third day. Bile appears to occupy an exceptional position, especially when inoculated by the subdural route, the two pigs so inoculated with a drop, about 0.05 c.c., of bile exhibiting signs of excitation of the motor areas of the cortex, dying within twenty-four hours, and showing the typical lesions in the lung, liver, and kidney in the most extreme degree seen in these experiments, whereas three control pigs inoculated subdurally with the bile of a healthy pig, and in doses from 0.05 c.c. to 0.15 c.c., did not show these symptoms, and survived without disturbance of the normal temperature curve. The entire contents of the gall-bladder, 0.3 c.c., when injected intraperitoneally, produced the typical illness in highly enhanced form, but had not caused death at seventeen days, when the pig appeared to be recovering. It is of moment to recall that the recovery of the organism from the bile, and also from the pig inoculated by

means of it, has already been recorded above. The occurrence of what were apparently meningeal symptoms has been described for the first monkey inoculated, and the second monkey also appeared to suffer from a toxic rather than an organismal action, if this distinction be permissible at this early stage in the investigations. The early onset and severity of the symptoms in guinea-pigs inoculated subdurally with the bile of infected animals suggests either that the organism is excreted by the liver and present in large numbers, or that the bile also contains some toxic products excreted by the liver. As already stated this organ is severely affected, the increase in size and other changes being expressions of the extent to which it has been called upon to function. It appears that the virulence of the organism is quickly enhanced by passage through a series of guinea-pigs. Whether or not this holds good for monkeys is uncertain. Whether or not the increased virulence can be maintained in cultures is of great importance, but remains still undetermined.

#### *The Microscopical Lesions.*

The tissues of all the seventeen pigs, including passage and reinoculation experiments, dying or killed, have been examined in serial sections. The outstanding lesions present a striking similarity to those usually found in the lungs, liver, kidney, and heart of man. The muscular lesion found sometimes in voluntary muscles, especially in the rectus abdominis, and vascular and nerve-cell lesions in the brain have also been encountered typically in one of the guinea-pigs allowed to die.

The following descriptions apply to the guinea-pig, since it was possible to obtain material in various stages of the disease. They are in agreement with the lesions found in the two, one primary and one reinoculation, monkeys killed.<sup>2</sup> At different times normal pigs have been killed to assist in the elucidation of the pathological processes, to exclude lesions not due to the inoculation of the virus of influenza, and to serve as controls to the foreign bodies and organisms present in the inoculated animals.

It is proposed to consider in detail only the lesions in the lung, and merely to refer briefly to those in other organs, such as the heart, liver, kidneys, brain, and voluntary muscle, since they will require detailed consideration in another paper dealing with nephritis. The lesions found in the heart are, however, of primordial importance in their bearing on the high mortality of the present epidemic.

*Lungs. Normal histology.* The microscopical structure of the lung in guinea-pigs presents certain peculiarities. The pulmonary artery when fixed has a very thick and often contracted muscular coat. The thickening is not always uniform, often being eccentrically placed in cross-section, due to a band of smooth muscle. The endothelial cells are crowded together by the contraction,

<sup>2</sup> In a nephritis experiment a lung lesion with adherent pleurisy was found associated with the presence of a round worm. There was no such intercurrent cause in the influenza experiments.

and have assumed strange shapes, often as if pseudopodia had been fixed while protruding into the lumen. The smaller arteries running out to the alveolar capillaries come off at right angles from these thick vessels, and, being devoid both of the thick muscular layer and of the band of smooth fibre, they present a strange contrast—appear dilated and their endothelium remains flat. The pulmonary vein has a very thin wall in comparison. The alveolar capillaries enter the smaller veins with abruptness. The vessels, but especially the pulmonary vein, are accompanied by lymphoid tissue often assembled as nodules in the angles where a smaller vein enters a larger one. In a cross-section of the bronchial tract this lymphoid tissue is usually between and around the artery and vein, but much more of it around the vein. It may obtrude into the areolar tissue. The mucous membrane of the bronchi is thrown into numerous rugae, which are exaggerated by the contraction due to fixation, and small round cells embedded in mucus are not uncommonly found in them. The areolar tissue also exhibits peculiarities, but by no means always. Patches of lung tissue imperfectly expanded and with thickened alveolar walls, such as is usual in the newly-born guinea-pig, may be met with, or there may be more dense areas of consolidation running out from a bronchiole or even a bronchus. In some cases there are old inflammatory foci containing giant cells. Various large cocci and bacilli may at times be detected in sections, and are easily recoverable on culturing guinea-pig lung.

Some of these areas of consolidation are, however, not of this origin; they consist of densely packed endothelial cells with only imperfect vascularity, and are probably due to defects in expansion and in the development of the capillaries. Small acute inflammatory areas have been met with in the healthy pigs killed, such as may have preceded the older inflammatory foci above mentioned. The elastic tissue is distributed around the bronchi and vessels and throughout the alveolar tissue as in man. It should be borne in mind that although the true eosinophil of the guinea-pig contains well-defined and deeply staining granules, the polymorphonuclear leucocytes contain little rods staining much more faintly, and having a striking resemblance to very small Gram-negative bacilli.

*General view at low-power magnification.* The lungs were fixed entire in formalin and then cut into sections which were transferred to other fixatives when necessary. They were stained by the ordinary haematoxylin, methylene blue, and eosin methods, and by Giemsa, Marchi, and Weigert's elastic tissue stain, &c. When one or both lungs are so completely involved as to resemble outwardly the complete consolidation of pneumonia, the nature of the process cannot be followed owing to the general disturbance of structure, caused apparently by widespread haemorrhages into the alveoli. Indeed, the disturbance, where of least extent in such lungs, was very much like that seen at the cut edge when a piece has been snipped off by a pair of scissors, or at best like the lung tissue adjoining a red infarct. When not filled with blood the majority of the alveoli were filled with a sero-fibrinous or oedematous exudate, which is relatively poor in fibrinous network. In two cases in the passage experiments there was on the contrary quite a lot of fibrin in the situations mentioned. The amount of sero-fibrinous fluids contained in the alveoli tends to be greater under the pleura and towards the bases of the lungs, so that a zone many alveoli deep may form a uniform groundwork in which the intensely engorged capillaries appear embedded, when they are not ruptured. Internal to this zone haemorrhage is the predominant feature.

Running in from the pleura, but usually more extensively under it, there are commonly portions of lung which are devoid of staining reactions; they are necrotic and obviously dead with or without collapse, as if cut off by thrombosis; but there is no reaction round them.

Areas of emphysema are commonly interspersed within or adjacent to such disintegrated tissue. These enlarged air spaces, infundibular passages, and even



bronchioles, are sometimes filled with what on superficial examination appears to be an imperfectly stained and coarse fibrinous network which is not common elsewhere. The emphysema, curiously enough, is not limited to the more distal portions of the lung. It may be quite irregular or most marked centrally.

The contraction of the arterial walls referred to in fixed lung of normal pigs is exaggerated in those inoculated with influenza virus.

The arteries and veins are all intensely engorged. The small veins may show evidence of early fibrinous thrombosis, or actually of complete thrombosis, at times even up to the hilus. In some veins there is distinct evidence extending to the hilus, of the leucocytes leaving the axial stream to lie along the vessel walls, while yet other veins contain no blood. As a rule, leucocytes are very scanty in the blood.

The bronchi may be of normal appearance, or the entire wall disintegrated by haemorrhages of various dimensions, but even the larger may show proliferation and thickening of the epithelium, often combined with shedding, and bronchi may be found plugged with epithelial and other cells embedded in a sero-fibrinous exudate, to an extent not met with in the lungs of the normal pigs killed. The relative absence of polymorphonuclear leucocytes and abundance of mononuclear cells is striking. Sometimes blood is also present in small or large amount, but by no means always. The smaller bronchioles, where they branch into infundibular passages, are often the most deeply affected; they may be surrounded by extensive haemorrhages, and disintegration of the muscular coat in whole or part is common. The same applies to the elastic lamina.

The walls of the arteries and veins appear to be similarly involved, showing haemorrhages into the muscular coat of even the largest arteries, rupture of the walls of smaller arteries, and extensive proliferation of the endothelium. Similar appearances are more common in the veins; but in them the homogeneous, if vacuolated, appearance of the vessel wall is more characteristic, and is more frequently associated with haemorrhages. The lymphatics in the bronchial tracts are distended with fluid-containing cells; in some instances they have been ruptured, their contents then running along the walls of the veins. The general impression made by low magnification is that of an acute vascular disturbance rather than of an actual inflammatory reaction with its sequelae, viz. the pouring out of fibrinous exudate and polymorphonuclear cells, the absence of both of which are in striking contrast with the pathological processes usually associated with disease of the lung, e.g. pneumonia.

These features are blurred in the severe forms of the lesion, and therefore are not marked in Fig. D, which is from a less severe case; it shows the extreme congestion with haemorrhage into the alveoli and consolidation due to the proliferation of the alveolar walls. The bronchioles are plugged with desquamated and proliferated epithelium. There is an indication of proliferation of the endothelium of a branch of the pulmonary artery. Fig. F shows the participation in the congestion of an old area of consolidation or more probably of unexpanded lung, with small haemorrhages, active phagocytosis of red cells, proliferation of endothelial cells, slight excess of polymorphonuclears and eosinophils, but more of mononuclear leucocytes.

*Detailed examination.* On more careful examination with high magnification the trabeculae between the alveoli are found to be notably thickened, very cellular, and the capillaries disorganized. The chief cause of the thickening is that the vascular epithelium has proliferated. The endothelial cells may be found *in situ* and covered by an exudate (Fig. G). In fortunate longitudinal sections of capillaries and veins the cells forming the endothelial pavement of the wall may appear pitted as if corroded, this appearance corresponding with the vacuolation seen in cross-section. The elastic tissue of the alveoli is fragmented, split up, and widely separated by the all-pervading exudate and cells. Patent capillaries are met with apparently functioning; others are functioning



imperfectly, and contain either beginning or already formed fibrinous thrombi containing a few red cells, as in Fig. L. As a rule, however, these details are blurred by the pervasion of the walls of the alveoli with fibrin and haemorrhages, there being a sero-fibrinous exudate applied as a layer to the endothelium of the alveoli or filling them completely over small areas. The exudate into the alveoli, while very extensive in severe cases, may occur only in scattered areas, as in Fig. G. Its structure is homogeneous. It stains like the plasma and contains few or no fibrin fibrils in contrast to the amount present in the alveolar walls and numerous smaller vessels which are thrombosed. This contrast between the homogeneous exudate in the air spaces and infundibular passages, and the fibrinous exudate within the tissues, is very striking. The fibrinous thrombosis of the radicles of the pulmonary vein is shown in Fig. L, together with the irregular proliferation of the vascular endothelium, and infiltration of adjoining connective tissue and alveolar walls with oedematous (sero-fibrinous) exudate. This fluid is encountered universally; it may adjoin the muscular coats of the vessels, bronchioles, and larger bronchi, and is even found under the epithelium of the bronchioles. The smallest bronchioles seem to bear the brunt of the process, their epithelium proliferating and desquamating, and the muscular coats losing their nuclei or becoming oedematous, vacuolated, and even ruptured. Their terminations are frequently the seat of minute haemorrhages or deposits of fibrin, as in Fig. D.

In contrast to the veins the smaller arteries are not affected to the same extent; but they do not escape, as Fig. D shows. The endothelium may be more or less lost, and even the internal elastic lamina irregularly thickened or its layers separated; actual rupture of the elastic lamina may take place. On the whole the arteries are functioning better than the veins. The haemorrhages can commonly be associated with thrombosis or destruction of a vein in an area to which the arterial supply has still been proceeding. The thrombosis of the alveolar capillaries may, however, only proceed as far as the first venous radicle, as in Fig. L, where the blood is obviously still circulating, although the vascular endothelium and the muscular walls exhibit signs of proliferation and vacuolation. The normal appearance, as if the muscle cells were laid down in circular layers, may be replaced by a homogeneous, almost necrotic appearance. This condition of the veins is shown to a more marked extent in Fig. L, where also the vacuolation is more evident. The irregular proliferation and vacuolation in the artery walls is shown in Fig. G, where the capillary radicles of the bronchial artery show marked proliferative occlusion; indeed, in severe cases, the extent of the haemorrhages into the muscular walls of arteries, veins, and bronchi or around them is a prominent feature, and always the most minute vessels appear to suffer first. Indeed, in the pig killed with the mildest or earliest form of the disease at a time when recovering (Fig. L), beyond a few small haemorrhages and localized areas of congestion the only departure from the normal was the thickening of the trabeculae over wide areas apparently due to proliferation of the capillary endothelium.

*Heart.* In addition to the small haemorrhages visible with the naked eye, others were found pervading the walls of both the right and left ventricles. In those of smallest dimensions capillaries were found again showing proliferated endothelium, and frequently accompanied by an undue number of round cells. The muscle fibres were often much vacuolated or had lost their striation; there was sometimes fluid between the fibres; staining by Marchi showed minute fatty intracellular degeneration running the length of some fibres over a wide area, while in other areas the Marchi reaction was entirely absent.

*Liver.* The liver was engorged, the cells very swollen and vacuolated. Frequently the nuclei stained poorly or not at all. Marchi's stain showed the enormous amount of fat present. Although there was much in the cells around the central vein the accumulation reached truly enormous dimensions

towards the periphery of the lobules. In one case (Pig F) which survived for ten days after the injection of 2 c.c. of culture into the mesenteric vein, the microscopical picture might be taken for that of acute yellow atrophy.

*Kidney.* In five out of the nine pigs which were killed or died after primary inoculation there was distinct evidence of acute congestion and early acute glomerular and tubular nephritis; in the case of one monkey killed the clinical evidence of nephritis was confirmed microscopically. Fig. F shows the kidney of a guinea-pig dead forty-eight hours after the intravenous injection of 1 c.c. of subculture of six days' growth. There is acute congestion with haemorrhages between the tubules. Three glomeruli show various phases of congestion, proliferation, and occlusion. The capsule of one glomerulus is filled with an acute exudation. There are earlier changes in the epithelium of the convoluted tubules. Such a nephritis of slight extent was replaced in the passage and reinoculation experiments by one of extreme gravity: all nine pigs which were killed or died showed this effect on the kidney. Within twenty-four hours of subdural inoculation the kidney in three out of the five cases was so engorged with blood as to recall the effect of tying the renal vein and the tubular epithelium so damaged as to remind one of the effects of mercuric chloride. There was extensive thrombosis of the venous and capillary system and vascular lesions analogous to those described in the lung. As the subject of nephritis must be reverted to in detail on another occasion, the foregoing description may suffice for the present.

*Brain.* Lesions in the brain were encountered most typically in Pig N 3, inoculated in the first instance subcutaneously and thereafter subdurally on two occasions, 51 and 16 days respectively elapsing between the second and third inoculations of culture. The pig died suddenly 38 days after the third and 105 days after the first inoculation. At post-mortem examination the brain seemed wetter than usual, but if this was so there was nothing else to attract attention. The brain was cut in transverse halves, fixed in formalin, cut in serial sections, and stained with methylene blue and haematoxylin and eosin. The sections show slight leptomeningitis together with a patchy infiltration of the outermost layer of the cortex with round cells, thickening of the wall, and sometimes thrombosis of the meningeal arterioles the walls of the veins being spared; although they are also accompanied by round cells. The arterioles running down into the brain often show thickened hyalin walls. Sometimes they are thrombosed and more rarely in process of occlusion by the proliferated endothelium. They may be accompanied by an excess of round cells. Such thickened arterioles in the depths of the brain may have their walls almost homogenous, except for the extensive vacuolation and the degenerated, shrunken, and scanty endothelial cells, and may have ruptured. The picture is an exaggeration of that described for the vessels in the lungs. The capillaries branching off from such arterioles may appear normal, except that they are accompanied by a moderate number of round cells, and contain red cells as in circulating blood; but they may be ruptured, although rarely.

The outer layer of the cortex, in addition to the excessive presence of round cells, is unusually widely meshed as if oedematous. The several layers of nerve cells show extensive degeneration, much more than can be ascribed to the post-mortem changes during a very cold night, and at most fourteen hours after the pig showed no particular departure from its chronic ailing health. The most striking feature is the extensive vacuolation of the cytoplasm and at times even of the nucleus of the nerve cells. The cytoplasm is so extensively vacuolated that the arrangement of the tigroid substance is unrecognizable,—there being very little that stains in the cytoplasm either with methylene blue or haematoxylin:—the nucleus, on the other hand, appears homogeneous and overstained. The nucleus contains either a very large swollen nucleolus or more than one, and sometimes a knob is added on to each side of the transverse section of

the nucleus as if it had lost its normal spherical shape. In the nucleus there are other small bodies of which the nature is less certain. In the cytoplasm there are usually round bodies, the largest about  $2\ \mu$  in diameter and others much smaller. They are vaguely stained by haematoxylin, but are brought out clearly by methylene blue, being more lightly stained than the nucleus or nucleolus. There may be one or many of these bodies, and, although often surrounded by a halo, they are not always contained in a vacuole, as in the case of Nigri's bodies in rabies. There is thus evidence of extensive involvement of the brain in association with a vascular lesion similar to that found elsewhere, and equally interesting perhaps is the demonstration of cell inclusions or degenerations not very dissimilar from those most familiar in diseases so widely removed as rabies and cancer.

*Voluntary muscle.* Obvious lesions of the voluntary muscles were not found except in the pig above alluded to, although on holding the abdominal wall against the light small haemorrhages were at times noted. In Pig N 3 there were distinct haemorrhages and a curious mottled appearance of the anterior abdominal wall. Microscopical examination yielded a reproduction of the lesion found in man and illustrated for the first time in Fig. K. This figure of the human rectus abdominis shows extensive and minute haemorrhages, proliferation of the capillary endothelium, vacuolation and loss of striation of muscle fibres, many of which are also fragmented, together with proliferation of round cells and of sarcolemma cells: both the latter are found in mitotic division. This state of affairs was also present in the pig, and moreover capillaries and arterioles completely occluded by proliferative endarteritis were included in the areas so affected.

*The organism in the tissues.* In the lung the organism is Gram-positive; but the deposit arising in the procedure opens sources of fallacy exaggerated in the case of so minute an organism. It is stained also by Giemsa, dilute fuchsin, and methylene blue and eosin, and is most certainly recognized as a minute coccus or diplococcus, i. e. the minutest forms seen in cultures situated in the alveolar endothelium and in the wall or in the neighbourhood of the alveolar capillaries. It may occur in short chains of three, and there may be little groups. It is most frequent in the proliferated capillary endothelium of the thickened trabeculae and other mononucleated cells. It has been seen in the subendothelial tissue of a vein and lying under the exudate in a bronchus. In the polymorphonuclear cells it has not been recognized. Some of the emphysematous infundibular passages and alveoli are filled with what at first sight suggests fibrin; but it does not give the staining reactions, and on close inspection has not the structure of a fibrin network. In association with these curious plugs, there may be minute bacillary organisms comparable with those seen in culture, and such plugs strongly suggest a close similarity between the glairy mucoid ground substance in the bronchioles and the ground substance in old cultures, in which minute coccoid bodies stand out in both. This comparison is best effected by staining with dilute fuchsin or even eosin alone, and then using a blue illumination.

In post-mortem material from man, there was no difficulty in demonstrating the organism, e. g. in the kidney of a severe case complicated by nephritis. The material was obtained twenty-four hours or more after death, placed in ten per cent. formalin, and also subsequently in alcohol-sublimate. The organism was Gram-positive, and readily found on employing Giemsa or the eosin-methylene blue method. It occurred in the cells of the convoluted tubules, either singly or as a diplococcus, sometimes in a row of three or a small group of four or more. In some glomeruli it was very numerous in the capillary walls, especially round the margin of the tuft within the capsule, in the capsule itself, and in the walls of the vessels, especially in the remains of the intertubular capillary network.

The presence of inclusions in the nerve cells of the brain has already been referred to.

*Conclusion from histological investigation.* It is well known that although the vessels as a whole remain well preserved after death, the endothelium is almost always lost, or if not desquamated and irregular. Fluid from the clotted blood transudes into the inner layers of the vessel walls. Many of the appearances in vessels described above recall appearances seen in man in tissues obtained at post-mortem examinations, but they are none the less interesting and important on that account, for post-mortem changes are excluded in the observations. The microscopical lesions of the lung are all referable apparently to an injury to vessels, especially to the lining endothelium, which is the only element common to the capillaries and other vessels. A chain of other vascular disturbances and muscular degenerations follows on the intense action on the capillary walls. Even the large vessels and bronchi, and in short all the tissue of the lung, may be involved. The fluid pervading the lungs may be partly a pressure oedema due to arteries remaining patent where veins are closed, and partly due to the squeezing of fluid out of the all-pervading fibrinous clots in the trabeculae and veins, the permeability of which has been altered.

The difference in the oedema exudate or transudate in different areas shows that more than one process is in play. The vascular lesions are not limited to the lung, but extend to all the organs described; after the lung they have been most strikingly evident in the kidney, where they play a large share in the acute nephritis which may supervene. They are also prominent in the brain.

The prolonged stay of the organism in the blood may stand in some relation to the extensive action on the vascular endothelium, and nevertheless be a toxic rather than a direct action of the organism. Hitherto much has been obscure in the pathology of the vascular system, and there is confusion not only regarding the bearing on one another of the several microscopical changes recorded, but also as to the sequence of events observed during life. Very little, however, is known of the earlier stages which precede the obvious changes observed clinically or found histologically in vessels. Since several of the organisms associated with diseases now undergoing investigation appear to have similar or nearly related actions, the more detailed study of their nature is left over to be resumed when a wider outlook has been obtained.

#### *Effects of Reinoculation.*

Up till now this has been possible in the case of one monkey on which intravenous inoculation was performed twice via the femoral vein. The immediate effect of the second inoculation was very mild and transitory compared with the first (see Experiment 2, Monkey D) or that in the control monkey. Subsequently, however, the animal fell off in health, and during the succeeding three months gradually got worse and was ultimately killed, when it resembled a monkey dying from tuberculosis.



*Post-mortem Notes, March 29, 1919.*

Subcutaneous fat present. Nothing of note in abdominal wall. Stomach empty, few dark spots as if old haemorrhage, recent haemorrhage in large intestine. Liver very large, pale, and mottled. Kidney large, capsule adherent, on section suspicious. Considerable fluid in abdomen. Chest: heart very large, flabby, especially right ventricle, pale seemingly old lesions, no pericardial fluid. Lungs: no tubercle, very emphysematous, apparently old scattered lesions, and some recent discoloration at base and posteriorly. Lungs whole into formalin. Skull: under dura there was a slight excess of fluid, pia-arachnoid slightly milky (?) These lesions were typical of influenza as described in preceding pages, and sufficient to ascribe the ill health of the animal to the effect of the inoculations.

Microscopical examination confirmed these findings, the old and recent lesions of the lung, but especially of the heart, sufficing of themselves to explain the animal's unwillingness to move. There were much slighter changes in the kidney than expected. The nervous system showed very slight changes as compared with those described in the guinea-pig. The posterior root ganglia of the cervical enlargement were infiltrated with round cells in some areas but not in others. The organism was detected in the lung. In guinea-pigs the results of six preliminary inoculations are recorded. Repeated subcutaneous inoculation produced no obvious effects. After a preliminary intravenous or subdural inoculation another subdural inoculation gave the higher temperature curve shown. The temperature charts resemble those seen in some cases of relapse in man; whereas this was not so after a preliminary subcutaneous inoculation in pigs. A comparison of the temperature of the three pigs which served as controls to the reinoculations is interesting. There was a corresponding contrast in the symptoms: a preceding subcutaneous inoculation seemed to modify the course of the disease favourably. Nevertheless all three pigs which were inoculated for the third time died, one within twenty-four hours, and another, being moribund, was killed after twenty-four hours. The third lived in ailing health for thirty-eight days and then died suddenly. Of the three controls to the last subdural inoculation, two were killed at six and twelve days respectively, and the third allowed to remain alive. The contrast between the naked-eye and the microscopical lesions found in the animals reinoculated after a preceding intravenous and subcutaneous inoculation was quite unexpected. In one (Fig N 6), where the preceding inoculations had been first intravenous and then subdural, there was naked-eye lesion more marked than that in the controls. The lungs appeared solid and resembled those of lobar pneumonia. There were present the severe lesions described in the kidney and liver; whereas the control when killed at twelve days showed only moderate lesions. The lungs of the other two pigs inoculated in the first place subcutaneously showed nothing of note to the naked eye, and microscopically there was no evidence of the acute processes such as congestion, inflammatory exudate, and haemorrhages. There was evidence in both of an old small area of consolidation, and a generalized thickening of the trabeculae elsewhere, most of the trabeculae, however, containing functioning capillaries. The condition was very similar to that described for Pig L in Experiment 4. The liver and kidneys showed the severest forms of lesions. The pathogenic action had therefore been by no means altogether abolished by the preceding inoculation, although greatly modified as regards the severity of its incidence on the lung. The pig that lived the longest also showed the extensive lesions of the brain described earlier. Moreover, the organism was present in the lung tissue, the fact suggesting that antitoxic rather than bactericidal influences had been in play in modifying the course of the disease. It is interesting to note that this modification was present in both animals inoculated in the first instance subcutaneously, but absent in the pig in which

the first inoculation had been intravenous, thus following the usual law that the subcutaneous method is the most effective way of first inducing immunity when antitoxic reactions are in play, and notwithstanding that this mode of injection produces so mild a form of the disease that little or no noticeable result follows. The experiments are, however, too few to warrant far-reaching conclusions, and much remains to be done on the effect of freeing the culture media from organisms before the bacteriological questions raised can be settled.

#### *General Conclusion.*

The result of the experiments described may be claimed to establish that all the lesions of influenza have been reproduced in animals by the injection of pure cultures of an organism isolated from man, and to fulfil all the requirements necessary to establish that organism as the cause of the disease. It is important that the disease was reproduced in the first place in attenuated form as in polyneuritis. The increase in virulence by passage so that, e. g., the mortality in subdural inoculations rose from a probable four in six to a real mortality of three in three, and perhaps the fatal effects produced in all pigs reinoculated for the third time, may have a bearing on the greater severity of late phases of the present epidemic. The success of subdural inoculation and the rapidity of onset thereafter may give support to the opinion that the organism finds entrance to the body via the naso-pharynx, but does not exclude other means of entrance. The numerous sites in which the organism is found in the body, and its presence in the bile and kidney and also the urine of monkeys, show that the nasopharyngeal mucus is not the only channel of its excretion. The prolonged residence of the organism in the tissues may likewise be of epidemiological significance in the production of strains of heightened virulence.

The only explanation of the rapid constitutional and widespread tissue effects following subdural inoculation is that it speedily passes to the blood, producing primarily a septicaemia, and thereafter an extensive destruction of minute vessels with many secondary consequences. The whole of the finely co-ordinated mechanism which in health ensures both a uniform distribution of blood and of air throughout the vascular and air tubes of the lung is disorganized, in acute cases within twenty-four hours.

The grave state of the lesions at the margins and bases of the lungs is probably not the direct action of the virus or its products, but largely mechanical. The dead inelastic but porous tissue in a still expanding thorax occurs at the sites where the respiratory movement of the lung is greatest, and this factor largely determines the greater filling of the alveoli and tissues generally with blood and transuded fluid or oedema at the margins and bases of the lungs. It becomes also a matter for consideration in how far this mechanical factor, combined with the disorganization of the physiology of respiration, determines the early gravity of the lung lesions as a whole, to the exclusion of a specific action on its capillary endothelium.

While there is evidence that the effects occur more rapidly and severely in



the lung than in other organs, there are departures from this general rule, and it has been possible by experimental means to obtain partial, indeed very good, exemption of the lung. Influenza should no longer be regarded as primarily a disease of the lung. The process is exactly the reverse. The lung is not attacked through the air passages by a gradual extension downwards from the higher respiratory passages to the alveoli. The lungs are attacked from within the body throughout their entire vascular mechanism from the blood-stream, in company with other organs in varying degree. Masses of dead or disorganized tissue and blood clot and the disorganization of respiration soon provide not only foci for local secondary infective processes, but also means by which the secondary infections, in their turn, come to produce septicaemia on their own account by a reversal of the process in an individual weakened by the primary disease.

Many points of general pathological interest bearing on a number of other diseases have arisen; their discussion is deferred, with allusion only to the possibility that the horizon hitherto limiting the outlook on disease and its investigation, prevention, or cure has been enormously extended, not only for the notoriously infectious and contagious diseases, but also for others where an infective agent has not been so much as suspected.

The work has been carried out in a laboratory situated in the partially re-erected old Surgical Observation Hut provided by the British Red Cross Society, who have furthered the work by indispensable assistance rendered through Major Abrahams and Capt. Lemming. Part of the money expended on the investigation has been derived from a grant made by the Trustees of the Beit Memorial Fellowship Fund.

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## BACTERIOLOGY

By J. A. WILSON

### 1. *Introduction.*

In a study of the recent literature on the pandemic of influenza, the most striking feature is the diversity of the bacteriological findings. In some investigations the bacillus of influenza has been isolated from the blood and sputum with great frequency, while in others, dealing with apparently the same type

of case, this organism has not been found, or has been found but rarely, the infection agents being pneumococci, streptococci, or less frequently the pneumobacillus. This diversity has led some writers to suggest the possibility of some undiscovered agent being concerned in the production of the fundamental lesions, and in most instances the suggestion has been that the causal agent is a filtrable virus.

That a filtrable virus was associated with influenza was first demonstrated by Nicolle and Lebaillly (3), who, by the subcutaneous inoculation into the human subject of a filtrate of sputum from a case of influenza, produced a febrile illness comparable with the naturally acquired disease. Graeme Gibson, Bowman, and Connor (4) repeated these experiments using monkeys instead of the human subject and obtained confirmatory results.

With regard to the exact nature of the virus, v. Angerer (5), using a glucose bouillon, cultivated a minute Gram-negative filtrable organism from the blood and tissues of fatal cases, and from the blood of experimentally inoculated rats. The organism grew aerobically and anaerobically. Similar results were obtained by Binder and Prell (6), the former, in addition, demonstrating the organism, microscopically, in the lung and other tissues.

The present investigation, commenced in October 1918, had for its primary object an attempt to demonstrate the presence of a filtrable virus in the blood of cases of influenza by cultural and experimental methods. Successful in this attempt, the scope of the inquiry was widened to include the examination of the sputum and other material which might be available from the complications of the disease. In all, sixty cases have been investigated, and the specimens examined in connexion with them may be stated in the following table:

A. Blood, sputum, and pleural fluid in . . . . .	4 cases.
B. Blood and sputum . . . . .	9 "
C. Blood only . . . . .	11 "
D. Sputum and pleural fluid . . . . .	8 "
E. Sputum only . . . . .	19 "
F. Pleural fluid only . . . . .	4 "
G. Blood and urine . . . . .	1 "
H. Blood and post-mortem tissues . . . . .	1 "
I. Cerebro-spinal fluid and post-mortem tissues . . . . .	1 "
J. Post-mortem tissues . . . . .	2 "

## 2. *The Preparation of the Specimens for Culture.*

*A. Blood.* The withdrawal of the blood is accomplished in the usual manner, ten to fifteen cubic centimetres being obtained from a vein in the arm, and added to an equal volume of sterile 2 per cent. sodium citrate in normal saline solution. For cultural purposes the 'whole' blood, the plasma, or washed

red corpuscles may be used. When it is not convenient to put up the cultures on the day on which the blood is withdrawn, it should be added to an equal volume of 50 per cent. glycerin in citrated saline.

B. *Pleural fluid and cerebro-spinal fluid.* These two fluids may be considered together. A portion of the fluid is centrifugalized, and the sediment examined microscopically to determine the presence, or otherwise, of an additional infecting agent. If there is no evidence of other infection, the fluid may be used in its natural state, or it may be centrifugalized and the sediment taken for this purpose; but the latter method has the disadvantage of increasing the risk of contamination. When other organisms are present in the specimen it may be filtered, or the sediment may be emulsified in three volumes of the 50 per cent. glycerin solution, and allowed to stand at room temperature and in the dark for three or four days, when the culture may be put up.

C. *Sputum.* The sputum is collected in sterile vessels. The most satisfactory method of excluding the other organisms present is to filter the specimen in its natural state, or, if it be too glutinous, after emulsification in normal saline solution, through Berkefeld N or V filters, these types being found most suitable. When large numbers of sputa are under observation, the strain on the filters is a heavy one, and it becomes necessary to resort to the glycerin method, one part of sputum being emulsified in three parts of 50 per cent. glycerin. In the early stages of the disease the sputum contains comparatively few other organisms, so that after a period of three or four days the emulsion may be used for cultural purposes. Later on in the disease, notably after the development of broncho-pneumonia, the glycerin process may require as long a period as ten days, and even then may fail owing to the presence of certain glycerin-resisting sporing bacilli. It is therefore safest, in the case of sputum from a broncho-pneumonia patient, to filter the specimen at the outset.

D. *Urine.* The sediment obtained by the centrifugalization of a catheter specimen is employed. It is sufficient to emulsify it in glycerin as in the case of the sediment from a pleural fluid.

E. *Post-mortem specimens.* Such specimens are usually grossly contaminated with sporing bacilli, and therefore unsuitable for treatment by the glycerin method. It is necessary, therefore, to emulsify them in normal saline solution, and to filter as in the case of sputa.

### 3. *The Preparation of Cultures.*

The method adopted in the isolation of the organism is that introduced by Noguchi (7), some years ago, in the cultivation of the globoid bodies of poliomyelitis and subsequently applied by the writers in the case of the organism of infective polyneuritis (8). It is not proposed to repeat the details of the technique, but reference may be made to certain points which, it is thought, are of practical importance in the present investigation.

The bouillon is made from beef or mutton, not from a commercial meat extract. It, and the 2 per cent. agar, have a reaction of + 10 on the Eyre scale.

In the case of the serum factor of the medium, human serum and horse serum give better results than the sera of guinea-pigs and rabbits. It should be inactivated and sterilized by heating at 56° C. for two hours on three successive days.

The animal tissue employed is the kidney of the rabbit, not because of any superiority over that of the guinea-pig as a cultural element, but simply from the fact that, being larger, it permits of a greater number of cultures being put up. Other organs, such as the liver and spleen, are unsuitable in that they are so frequently contaminated.

Cultures of the blood, pleural fluid, and cerebro-spinal fluid are put up in conical Erlenmeyer flasks of fifty cubic centimetres capacity. It is not advisable to put more than ten cubic centimetres of blood or other fluid into each flask, the amount of melted agar required being about fifteen cubic centimetres. In the case of blood and pleural fluid, ordinary agar and broth are used; it is only in the case of cerebro-spinal fluid that the serum constituents must be added. For a flask culture, the size of the rabbit tissue required is about  $\frac{1}{2}$  inch square.

Sputa, sediments, filtrates, and subcultures are put up in test-tubes  $6 \times \frac{5}{8}$  in size, a few drops of the fluid being added to each tube. In every instance it is necessary that the serum constituent should be present.

Lastly, it is essential to put up a series of controls embodying every material employed in the medium.

#### 4. *The Characters of the Growth.*

The characters of the growth present certain differences, dependent on the nature of the material under examination, but these are, for the most part, differences in time of appearance, rather than of quality.

In the case of 'whole' blood or of washed red corpuscles there is no obvious change in the medium, with the exception, perhaps, of a slight separation of peptone in the bouillon, until the fourth or fifth day, when minute yellowish colonies make their appearance on the surface of the blood and agar mixture. These minute colonies rapidly increase in size, and becoming confluent on the sixth or seventh day, form a faint yellow, continuous, and moderately adherent layer, showing slight ridging of its surface. At this stage there is usually quite a marked diffusion of haemoglobin through the bouillon. About the eighth day the blood and agar has become perceptibly lighter in colour and brownish irregular patches of growth may be observed in it along the base of the flask. There is no turbidity produced in the bouillon by the growth.

Owing to the transparency of the medium, plasma cultures, or cultures of pleural fluid, show evidence of growth as early as the third day, and it takes the form of a fine granular haze to be seen in the vicinity of the rabbit tissue.

A similar haze is seen in control cultures, but it does not appear until the fifth day, and is due to the change of reaction produced by the autolysis of the kidney. The haze becomes intensified, and spreading throughout the agar, it reaches the surface on the fourth or fifth day. The appearance of the surface growth is dramatic, and it is confluent almost from the outset. As in the case of 'whole' blood the growth does not extend into the bouillon to any degree.

Sputa, sediments, and filtrates usually show evidence of growth by the end of the second day, by reason of the larger number of organisms present. With this reservation, the changes are along the lines indicated in the case of a plasma culture.

With regard to subcultures, the growth appears as minute greyish-white colonies in the substance of the serum agar after forty-eight hours' incubation. The colonies unite and convert the serum agar into a greyish-white opaque mass. By the fifth day the surface growth is established. Two days later the serum agar has assumed a dirty brown colour, while the surface growth forms a moderately adherent layer about one-sixteenth of an inch thick, and greyish-white in colour. In third generation subcultures the surface growth is not a prominent feature, while in the fourth generation the organism usually dies out.

#### 5. *The Conditions of Growth.*

It will be observed that the conditions of growth are of a specialized character. Attempts to obtain cultures by the simpler and more familiar methods forming the routine of a laboratory have invariably failed. In subcultures growth can be obtained in a medium in which the serum is replaced by glycerin in the proportion of five per cent., but this modification is not so useful in influenza as it is in the case of certain other filtrable organisms, e. g. that of trench fever.

At the suggestion of Captain Bashford a medium was used in which one per cent. of sodium taurocholate was added to the serum agar and serum broth. No growth occurred in primary cultures, though a slight growth did occur in subcultures, but it was not such as to make the method of practical value. The result is interesting in the light of his passage experiments.

The organism is anaerobic, and remains so in subculture. Growth only takes place at the temperature of the body.

#### 6. *The Microscopic Characters.*

In films prepared from cultures the organism has the appearance of a minute, rounded, or slightly oval, undifferentiated coccus-like body, arranged in colonies of twenty to sixty elements, the individual elements showing sometimes a tendency to occur in pairs. It shows a considerable variation in size, the smallest forms being 0.15 of a micron, the largest 0.5.



In young cultures, that is cultures after four or five days' incubation, the small forms predominate. The larger forms sometimes seen are probably produced by the overlapping of two elements. In older cultures large forms predominate, and there is no doubt they are single elements, and are in the nature of involution forms. In the process of involution the organisms lose their staining properties, become indistinct in outline, but even in cultures fourteen days old one or two apparently normal forms can be seen in what is regarded as a degenerated colony. Involution does not take place with the same rapidity in cultures grown in the glycerin medium.

In the tissues the organisms show a similar appearance, though the tendency to occur in pairs is more marked. In the blood they are found free in the plasma, and also in the mononuclear leucocytes. In the sputum and in the pleural fluid the aggregation into small clumps is a marked feature, but they are also to be found in the mononuclear leucocytes and endothelial cells. In the tissues there is sometimes a suggestion of a capsule, but it is considered to be of accidental production.

The organism presents certain difficulties in staining. Little effect is produced by the ordinary dilute solutions of aniline dyes, even when applied for long periods. With Giemsa's stain applied for twenty-four hours, the organisms stain a dark purplish blue, but the preparations are not satisfactory owing to the staining of the background. Good results have been obtained by washing the films, after fixation in methyl alcohol, in ether for two minutes, thereafter staining in one per cent. methylene blue, or better in Kuhne's blue, for one hour. In young cultures the organism retains the stain in Gram's method; old cultures show a predominance of Gram-negative elements. The organism is not acid-fast.

In exudates satisfactory films are obtained by Gram's method of staining.

#### 7. *Filtrability.*

One of the salient features of the organism is that it passes through bacteriological filters. The types of filters employed in the present investigation are the Berkefeld N, the Berkefeld V, and the Massen porcelain filter. In the preparation of such filters for experiments, they should be scrubbed with soft soap and water, then immersed in distilled water made slightly alkaline with caustic soda. The water is changed every day for a week, when pure hot distilled water is run through the filters under pressure. The final stage in the preparation consists in boiling them in pure distilled water for three hours.

In the process of filtration advantage is taken of the negative pressure produced in an autoclave which has been raised to a steam-pressure of twenty pounds to the square inch and then allowed to cool, a method suggested by Private J. F. Graham. By a series of Y-tubes and stout rubber tubing several filters may be connected up to the exhaust nozzle, and in this way a great deal of labour is saved.



The first point to determine is the degree of permeability of the filter in use, and it is necessary to be certain that it is not permeable to ordinary bacteria. Satisfied that it is not permeable to these, it is then determined what size of body it will permit to pass through, and this is accomplished by a prolonged centrifugalization of the filtrate. The upper layers of the fluid are pipetted off, films made from the residue obtained, and measured with an eye-piece micrometer. In this way it is found that as far as filtrable organisms are concerned the letter applied to a filter by a manufacturer is no indication of its efficiency, it is only an index of the method of preparation. The two types of Berkefeld in use were generally found to be of the same standard, in that they permitted bodies up to 0.5 of a micron to pass through them. The Massen filters, on the other hand, were sometimes of a very high standard, one filter of this type being obtained which did not allow an organism larger than 0.1 of a micron to pass through.

The time required varied considerably. In the case of Berkefeld filters, sufficient for cultural purposes may be obtained in one hour. The Massen filters, on the other hand, require a longer period, as a rule about four hours. It is always advisable to discard the first portion of the filtrate. The organism of influenza passes through these three types of filters. It has been seen microscopically in the filtrate, it has been cultivated from the filtrate, the culture so obtained being used for the experimental reproduction of the disease.

#### 8. *Resistance to Certain Agents.*

The influenzal organism is resistant to heat, a property which appears to be common to the group of filtrable organisms. In cultures and in tissues heated in a water bath 56°C. for thirty minutes, the organism was not killed. The thermal death point was found to be 68°C.

Another point of interest, and one which has already been noted, is its resistance to the action of glycerin. This character is not the marked feature that it is in rabies or in the poliomyelitic diseases, still it is sufficient to permit of its being put to practical use in the isolation of the organism. In fifty per cent. glycerin the organism dies in from twelve to fourteen days.

#### 9. *The Distribution of the Organism in the Body.*

The organism whose main features have been detailed above has been found constantly in cases of influenza. It has not been found in a series of over sixty controls drawn from cases of trench fever, encephalitis, and certain of the exanthemata.

During the early stages of the disease the organism is present in the blood, and can be recovered therefrom as early as twenty-four hours after the onset of illness. It persists in the blood until about two days before the declension of the fever. In only one of the cases was there an added infection, that being pneumococcal in character. The blood was studied in twenty-five of the cases,

the organism being isolated in culture in twenty-two of them. It can be recovered from the plasma as well as from the washed red corpuscles.

Similarly, the organism appears almost at the onset in the sputum. It is present in very large numbers, sometimes it is to be seen in almost pure culture. With the development of the broncho-pneumonia it is to a great extent masked by the secondary infecting agents, the pneumococci, streptococci, &c., but it is still easily identified microscopically. It has not been possible to determine the length of time it persists in the sputum after the patient's recovery. In the forty cases in which the sputum was examined the organism was recovered in every instance.

In fourteen of the sixteen chest fluids examined it was present as the only infecting agent, and sometimes it was present in considerable numbers. It persists in the fluid for long periods, gradually diminishing in numbers, and becoming intracellular before its complete disappearance.

The remaining two cases were empyemata, the associated organisms being pneumococci.

In two cases there was an influenzal nephritis; in one of these the organism was recovered from the blood and urine, while in the second the organism was recovered from the blood during life, and from the kidney post mortem.

The organism has been isolated further from the blood in a case of influenzal jaundice, from the cerebro-spinal fluid, where it was associated with a *Staphylococcus albus* in the production of meningitis, and from the blood in a case of ulcerative endocarditis.

In fatal cases its distribution is found to be very wide. It has been seen microscopically, and cultivated, from the lungs and related glands, from the heart, the liver, spleen, kidney, and in one case from the brain.

The table compiled by Major Clayton shows at a glance the relation of the bacteriological findings to the type of disease.

#### 10. *Bacteriological Diagnosis.*

At the onset of the disease blood culture is the only reliable method of examination. It is true that the organism can be seen microscopically in stained films of the blood, but it is a difficult and prolonged procedure, and even after a considerable experience it is not always certain.

With the advent of the sputum, usually on the second day, microscopic examination is sufficient for the purpose of clinical diagnosis.

The films may be stained by Gram's method or by methylene blue. There is no difficulty in finding the organisms, and their size, arrangement, and distribution would appear to be diagnostic. The same remarks apply to pleural fluids and other exudates.

For absolute certainty, of course, cultivation of the organism is necessary.

## CASES OF INFLUENZA FROM WHICH THE FILTER-PASSING VIRUS WAS OBTAINED.

No.	Name.	Type of Illness.	Blood Culture.	Sputum Culture.	Pleural Fluid Culture.	Other Material Culture.
(1) <i>Mild Group.</i>						
1	Barton	Mild respiratory symptoms	—	...	...	...
2	Kemp	"	—	...	...	...
3	Clark	"	+	...	...	...
4	Bray	"	+	...	...	...
5	Brown	"	+	+	...	...
6	McPherson	"	+	...	...	...
7	Tombs	"	+	...	...	...
(2) <i>Pneumonic Group.</i>						
8	Wright	Pneumonia	+	+	...	...
9	Jose	"	+	...	...	...
10	Lee	"	+	...	...	...
11	McKenna	"	+	+	...	...
12	Gander	"	...	+	...	...
13	Ringwood	"	...	+	...	...
14	Macaulay	"	...	+	...	...
15	Dudgeon	"	—	...	...	...
16	Pratt	"	+	...	...	...
17	Journey	"	...	+	...	...
18	Campbell	"	...	+	...	...
19	Kelloy	"	...	+	...	...
20	Blair	"	...	+	...	...
21	Gibson	"	+	+	...	...
22	Norman	"	...	+	...	...
23	Scammar	"	...	+	...	...
24	Woods	"	+	+	...	...
25	McGowan	"	+	+	...	...
26	Maisey	"	...	+	...	...
27	Marceau	"	...	+	...	...
28	Doherty	"	...	+	...	...
29	Flack	"	...	...	...	P.M. lymphatic glands. Positive
30	Watson	"	...	...	...	...

No.	Name.	Type of Illness.	Blood Culture.	Sputum Culture.	Pleural Fluid Culture.	Other Material Culture.
31	Herriot	Pneumonia with severe haemorrhage	...	+	...	...
32	Finlay	"	+	+	...	...
33	Baker	"	...	+	...	...
34	Galloway	"	...	+	...	...
35	Boyd	"	...	+	...	...
36	Cresswell	"	...	+	...	Lung and lymphatic glands. Positive
37	Letherby	"	...	+	...	...
38	Pisey	"	...	+	...	...
39	Ferry	"	...	+	...	...
(3) <i>Pleurisy Effusion Group.</i>						
40	Jones, Sergeant	Pleurisy and effusion	...	+	+	...
41	Taylor	"	...	...	+	...
42	Domingos	"	...	...	+	...
43	Dias	"	...	+	+	...
44	Dean	"	...	...	+	...
45	Kettles	"	...	...	+	...
46	McMillan	"	+	...	+	...
47	Young	"	...	+	+	...
48	Kelso	"	+	+	+	...
49	Godsley	"	...	...	+	...
50	Jones, Major	"	+	...	+	...
51	Whyte	"	...	+	+	...
52	Hobbs	"	...	+	+	...
53	Bailey	"	...	+	+	...
54	Devise	"	...	+	+	...
55	Adler	Empyema	+	+	+	...
(4) <i>Miscellaneous.</i>						
56	Mainwaring	Meningitis	...	...	...	Post-mortem specimens. Cerebro-spinal fluid. Lung. Brain. Lymphatic glands. Positive
57	Beveridge	Jaundice	+	...	...	Post-mortem specimens. Cerebro-spinal fluid. Lung. Brain. Lymphatic glands. Positive
58	Smithers	Ulcerative endocarditis	+	...	...	Brain. Lymphatic glands. Positive
59	Gage	Nephritis	...	...	...	P.M. aortic veg. Positive. Lymph. glands. Positive
60	Jackson	"	+	...	...	Urine. Positive P.M. kidney. Positive

11. *Summary.*

1. An organism, of definite morphological and cultural characters, has been isolated from cases of influenza.
2. It can be demonstrated in the blood, sputum, and other exudates, and in the tissues, post mortem, by appropriate methods of staining.
3. It belongs to the group of 'filter-passers', a group of organisms which pass through bacteriological filters. It has been seen microscopically in the filtrate and has been cultivated therefrom.
4. It has not been found in a large series of controls.

The writer would like to acknowledge his indebtedness to many who have been of assistance in carrying out the investigation. In the case of Pte. J. F. Graham, the laboratory attendant, the debt is indeed great. His careful attention to detail, his pride in the perfection of his media, his enthusiasm, made the work possible under the difficult conditions existing in a General Hospital in France.

## APPENDIX

CLINICAL NOTES ON THE CASES OF INFLUENZA FROM WHICH  
THE VIRUS WAS RECOVERED

By F. CLAYTON

The facts and impressions here related are based on the experience of a series of sixty cases, from which an organism with certain specific characteristics has been recovered.

*Clinical description.* Although several different types of influenza have been recognized and described, our experience in the present epidemic confines us to that concerned with the respiratory system, only very brief allusion being made to other forms of the disease. Thus from the data available it has not seemed possible to describe a gastric or a nervous type, but rather to regard symptoms and signs relating to these systems as secondary to the respiratory infection. Similarly, no attempt is made to detach a septicaemia group, although evidence of a severe septicaemia was frequently observed.

For the purpose of description four groups of cases are here considered according to their respiratory affections.

Group 1. Mild cases in which the upper part of the respiratory tract is alone affected.

Group 2. Haemorrhagic influenza.

Group 3. Influenzal pneumonia.

Group 4. Influenzal pleurisy with effusion.

*Group 1. Mild influenza.* In Group 1 the onset has for the most part been gradual, and the men have generally been ailing for three or four days before being admitted to hospital. The typical sudden onset has been exceptional. During these early days they have suffered from sore throat and a feeling of feverishness at night. Sometimes they describe their throat as feeling raw, sometimes as acutely painful; to account for this there is often surprisingly little to be seen in the pharynx. Rhinitis and coryza are constant, and are often followed by hoarseness and aphonia. The presence of neuralgic pain over one or both eyes seems to suggest that the frontal sinus often shares in the inflammatory process. In one case this pain over the frontal sinus was very severe and lasted for three days; pain referred to the other air sinuses is not so frequent or so severe.

These earliest symptoms are quickly followed by cough; this is short, dry, and explosive, often occurring in paroxysms. At this early stage there may be obvious cyanosis, usually slight in degree and unaccompanied by dyspnoea. Examination of the chest during the first forty-eight hours often gives negative results, or at most discovers the presence of a few fine râles at both bases. Sputum is often absent. The temperature at this time is usually 103° to 104° F., whilst the pulse-rate rarely exceeds 110 per minute.

In these mild cases a great change is usually found on the third or fourth day; the temperature has begun to fall, the cough becomes loose and more productive, and the patient's outlook is altogether happier. It is very often that physical signs in the lungs make their appearance for the first time during this stage, and consist of coarse râles without any impairment of note or any sign of consolidation. The sputum becomes plentiful and purulent. This, or even less than this, forms in many cases the extent of the local inflammatory process, and within a week the patient has recovered.

*Group 2.* In a large proportion of cases, however, the infection is much more severe and the inflammation far more extensive. The transition from the early stages just described to the grave state at present under consideration is frequently alarmingly sudden, and it is not uncommon for a case regarded as mild to pass into a serious condition and perhaps die within twenty-four hours from the occurrence of this change. Sometimes such a patient, without going through the condition described in Group 1, becomes suddenly and acutely ill after two or three days' fever without symptoms or signs. Often in the days preceding this acute haemorrhagic type he makes no complaint or sits up in bed quite comfortably; it is remarkable how cheerful many of these patients have been during this stage; the only sign that all is not going well is the persistence of high and sustained fever; the temperature is in fact well ahead of the symptoms and physical signs. The temperature chart in these cases is nearly always suggestive of lobar pneumonia, but, with this exception, the patient presents no features of the latter disease. Instead of being flushed, he is generally pale with a suspicion of cyanosis which may be quite easily overlooked; this early appearance of cyanosis contrasts with its late development in lobar pneumonia.



In both maladies it is a grave sign, and its rapid onset in the influenzal condition helps to emphasize how much more serious is this disease than the other. Dyspnoea is not a feature of these cases, and the pulse-respiration ratio is often little disturbed. Pain, a constant accompaniment of pneumonia, is usually absent here and the characteristic pneumonia cough is never heard. If symptoms are wanting at this stage physical signs in the lungs are even more so, and amount at the most to some impairment to percussion at both bases; no bronchial breathing or any sign of consolidation can be discovered.

The tendency to haemorrhage is, however, the most striking peculiarity of this group. It is very sudden in its onset, and is preceded by the expectoration of an increasing amount of watery sputum, rapidly becoming blood-stained, and in a few hours intimately mixing with an abundance of pure bright blood. Nose-bleeding often accompanies the haemoptysis. With the onset of this haemorrhage the whole aspect of the patient is changed; he becomes increasingly cyanosed and restless, and often passes quickly into a moribund state. Recovery in these very severe haemorrhagic cases is unusual.

*Group 3. Influenzal pneumonia.* There remain a number of cases in which this haemorrhagic tendency is not a feature and which may be appropriately classified under the heading of 'Influenzal pneumonia'. They present a very wide divergence from the fulminating haemorrhagic group just described, and on the other hand do not appear to be ordinary cases of lobular pneumonia.

After the first few days of slight initial fever and general disturbance (*vide* Group 1) they become acutely ill with high and maintained fever. In this group cyanosis is much more obvious than in Group 2 and is frequently intense; with it there is no breathlessness, and it is quite unusual to find any of these patients who will consent to being propped up in bed; they much prefer the completely horizontal position. With this cyanosis there is often great disturbance of consciousness. As a rule, this takes the form of delirium of a muttering type; it is never violent and the patient is never difficult to control; he is, in fact, prostrate as the result of his infection, and never displays the active delirium seen in pneumonia; there is a coarse tremor and occasional twitching of the limbs. In a minority of these cases of cyanosis there is profound stertorous and continuous sleep; the patient can easily be roused for food, &c., but readily relapses into his unconscious state when the need for its interruption is passed. Case II is an example of this type.

As in Group 2 the initial fever approximates to that seen in lobar pneumonia, being continuous and lasting for four to ten days; there is no crisis, resolution being gradually effected and the normal temperature being reached from ten to eighteen days after the onset of the illness.

The pulse-rate generally remains raised for some time after the temperature has started to fall, and it is often quite feeble even when complete recovery has taken place. That there is often a considerable degree of cardiac weakness after such an illness was shown by one of our patients who had a severe fainting attack

whilst sitting up in bed after his temperature had been normal for more than a week. In the acute stages it is quite usual to find the right limit of cardiac dullness extending well beyond the right sternal border.

Vomiting is a prominent symptom in the early part of the disease, and uncontrollable hiccough occurred in two of our cases, both of which terminated fatally. Diarrhoea was often severe and distressing.

The sputum after the first few days becomes profuse, purulent, and blood-stained, often remaining tinged when the patient is apparently convalescent. Herpes is quite uncommon. There was always during the febrile stage a slight degree of albuminuria. The knee-jerks are frequently lost; always diminished.

The physical signs in the chest are often very slight during the early stages, and sometimes throughout the whole illness very little can be made out by the ordinary routine examination. Percussion usually shows impairment at both bases, but seldom any actual dullness unless an effusion is present; the impairment is generally bilateral and is accompanied by weak breath sounds. Subsequently crepitant râles, increasing from day to day until resolution is nearing completion, are fairly constant; bronchial breathing is not so common, and when it does occur it is extremely limited in its distribution. Vocal fremitus is often much diminished, whilst vocal resonance remains unaltered. Skodaic or in fact any degree of hyper-resonance is not generally found.

*Group 4. Pleurisy with effusion.* This group includes a further stage into which many patients pass. The initial illness is often less severe than that described in Group 2, and there is frequently apparent recovery from this, when a gradual increasing rise of temperature demonstrates that the inflammatory process is not at an end. There is the usual sharp pain typical of pleural inflammation, and general constitutional disturbance.

Commencing dullness at the affected base and a few pleuritic crepitations are discovered; sometimes there is a coarse friction in the axilla. Breath sounds are absent or only faintly heard and often tubular in character; local fremitus is diminished and the diagnosis of pleurisy effusion is established. Although the amount of fluid often develops rapidly much cardiac displacement is unusual and was present in only one of our cases. The condition becomes essentially a sub-acute one, and lasts as a rule for about four weeks. Case III is a typical example of this group.

Exploration discovers the presence of opalescent fluid, sometimes pale or straw-coloured, occasionally green, and always more or less turbid. In two of our cases the fluid was frankly purulent, needing rib resection and complete drainage.

*Complications. Renal.* Two cases of the sixty in which the organism was found had renal symptoms. One had severe lumbar pain and albuminuria; a catheter specimen of the urine showed no casts or corpuscles, but the presence of the filtrable virus in great abundance. The other had definite acute nephritis occurring with the influenzal pneumonia. A fatal result attended this case, and both kidneys showed evidence of this.

*Nervous.* The organism was recovered from the cerebro-spinal fluid of a case of purulent meningitis both during and after life.

*Otitis media* was present in two cases, both of which were very severe.

*Thrombosis.* Femoral thrombosis has been seen on four occasions giving rise to considerable oedema.

*Malignant endocarditis* followed rapidly in an apparently ordinary case of influenza. The vegetations on the aortic valves showed the presence of the organism.

*Case I.* The following notes are typical of the Haemorrhagic Group.

Feb. 9, 1919. Major B. was admitted to hospital complaining of feeling feverish. For the past two nights he has slept badly, but has had no pain, and beyond an irritating cough and discomfort in his throat has nothing to report.

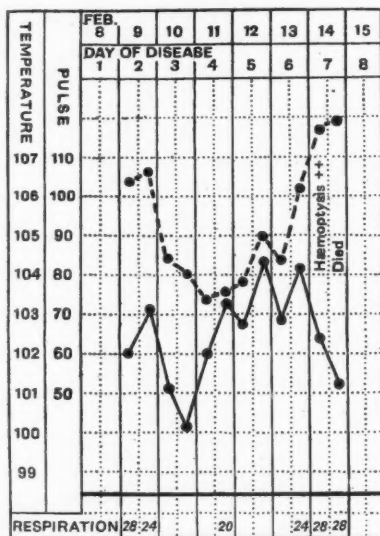


CHART I. Showing typical fever, with comparatively slow pulse and respiration rate.

He lies comfortably in bed; colour good. Temperature  $102^{\circ}$ . Pulse 104. Respiration 28. Tongue dry—conjunctivae red. No signs in heart or lungs.

Feb. 10. During the night cough has increased. Much abdominal pain. There is a little viscid sputum. Lungs seem quite clear. Temperature falling.

Feb. 11. In spite of relapse of fever last night he feels better. Cough less painful. No dullness or adventitious sounds in chest.

Feb. 12. Continued fever. There are a few scattered râles to be heard at both bases. Sputum is slightly blood-stained and more profuse.

Feb. 13. General condition unchanged. Breath sounds at both bases are weak.

Feb. 14. To-day there is cyanosis of lips and ears, together with increased respiration rate. Sputum is now mixed with bright blood. Moist sounds are heard in both lower lobes. Some dilatation of heart to right of sternum. 2.30 p.m.: Haemoptysis continued, and patient died. Post-mortem notes:

Two pints of blood-stained fluid in r. chest. Six ounces of blood-stained fluid in l. chest. No adhesions. Both lower lobes very engorged and oedematous; float in water. Heart muscle soft. Minute coccal bodies were found in sputum; also in lungs and lymphatic glands after death.

*Case II. Illustrating severe 'Influenzal Pneumonia'.*

Feb. 17, 1919. Pte. M., age 31. Admitted to hospital with history of pain in throat and chest for one day. Headache and pain in back also present. Patient is cyanosed—lies flat in bed. No dyspnoea. Tongue dry. Tonsils both enlarged. No exudate. Temperature  $103.4^{\circ}$ . Pulse 100. Respiration 24. Heart and lungs clear.

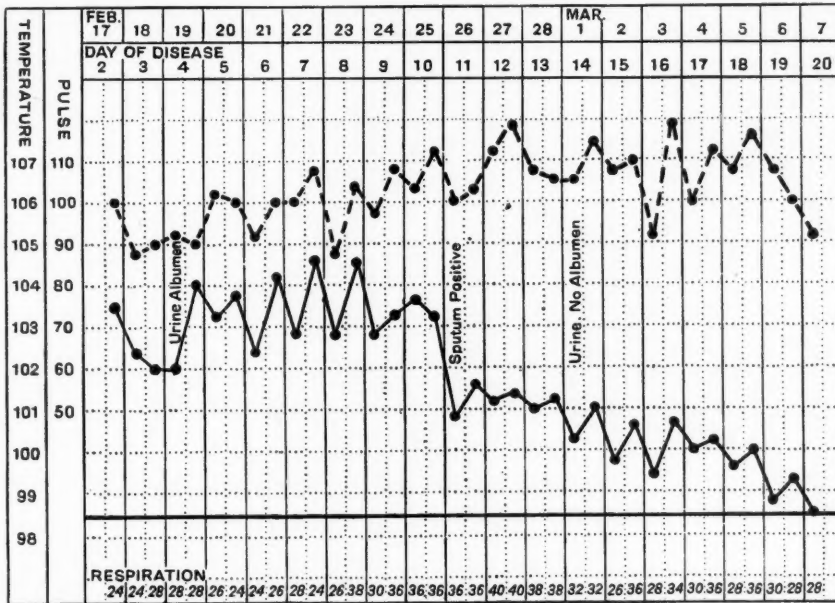


CHART II. Showing typical fever, prolonged resolution and continuance of pulse-rate. There was intense cyanosis. In the acute stage this patient was in a deep and stertorous sleep.

Feb. 18. Less fever—cyanosis remains. Cough with sticky sputum. There are no signs in the chest. Pulse good.

Feb. 19. Sputum slightly blood-stained. No dullness can be made out. Breath sounds at both bases are natural. Urine shows cloud of albumin.

Feb. 21. Continued high fever. Cyanosis has increased. Right base impaired. Weak breath sounds.

Feb. 22. Patient lies in a stertorous condition interrupted occasionally by bouts of coughing. He can be easily roused to take his food, but almost immediately returns to his unconscious state. Oxygen given continuously has improved his colour.

Feb. 27. Temperature has fallen, but pulse-rate and respiration-rate have increased. General condition is the same. Right base is dull, and there are abundant coarse crepitations to be heard. No tubular breath sounds.

Mar. 3. Temperature is slowly falling; pulse-rate still keeping up. Scattered râles both sides of chest. Sputum more profuse. Patient is less cyanosed and much more awake.

Mar. 7. Temperature has reached the normal line, and general condition has improved. Cyanosis has disappeared.

*Case III. 'Influenzal' Pleural Effusion.*

Jan. 29, 1919. Pte. B., age 21, was admitted to hospital with the following history. Pains in the right side of his chest ten days ago. Since then the pain has disappeared, but the patient has been feverish since. He was ill for a week in 1916 with similar pain. Breathing is not difficult. Temperature 100°, pulse 90, respiration 26, on admission. Patient is pale, and has a dry tongue. Right side of chest moves little—there is dullness behind and in front. No skodaic resonance. Breath sounds are not heard on the right side except at the apex. Right chest aspirated on day of admission—45 oz. opalescent fluid.

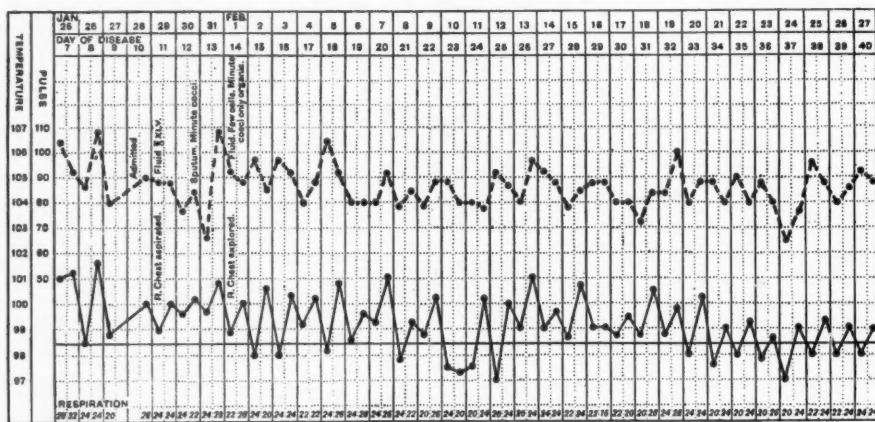


CHART III. Showing prolonged subacute condition.

Jan. 30. General condition unchanged. Some relief obtained from paracentesis and increased air entry into right lung. Sputum mucopurulent. No tubercle bacilli found.

Feb. 1. Right chest again explored—similar fluid obtained. The cells in this are very few, and these are mononuclear. Skodaic note at right apex.

Feb. 7. There has been irregular fever. Air entry into right lung is improving. Friction is present in right axilla. Left lung is clear.

Feb. 14. General condition is improving, though there is still slight fever. Breath sounds are now audible at a lower level than heretofore.

Feb. 21. Temperature has settled. The right side is still retracted, but movement is returning and breath sounds are better heard. Coarse friction at right scapular angle.

Feb. 28. No further rise of temperature or sign of relapse.

Pathological investigation. Minute coccal bodies found in pleural fluid and sputum.



## REFERENCES.

1. Pfeiffer, R., *Zeitsch. f. Hygiene*, Leipzig, 1893, xiii. 357.
2. Askanazy, Aschoff's *Pathologische Anatomie*, 3<sup>te</sup> Aufl., 1913, 157.
3. Nicolle et Lebaillly, *Compt. Rend. Acad. Sci.*, Paris, 1918, clvii. 607.
4. Graeme Gibson, Bowman, and Connor, *Brit. Med. Journ.*, 1918, ii. 645.
5. v. Angerer, quoted in *Medical Supplement*, No. 2, vol. ii.
6. Binder and Prell, *ibid.*
7. Noguchi, *Journ. Exp. Med.*, New York, 1911, xiv. 99.
8. Bradford, Bashford, and Wilson, *Quart. Journ. Med.*, Oxford, 1919, xii. 88.

## DESCRIPTION OF FIGURES.

FIG. A. Influenza virus (1) 3 days' growth; (2) 5 days' growth; (3) 7 days' growth.

FIG. B. Culture from sputum 5 days' growth (1)  $\frac{1}{8}$  in. obj. Baker; (2)  $\frac{1}{2}$  in. obj. Angus.

FIG. C 1. Lung of guinea-pig (natural size) showing appearance at death 7 days after subdural inoculation of 0.05 c.c. of bile from Pig M inoculated with culture of influenza organism. See Fig. C 2 (passage experiment Fig M 3). The left lung simulates the naked-eye appearance of pneumonia consolidation, the right lung shows typical broncho-pneumonia patches.

FIG. C 2. Lung of guinea-pig (twice natural size) killed 7 days after subdural inoculation of 0.05 c.c. of subculture of influenza organism (4 days' growth). The naked-eye appearances were similar to those shown in Fig. C 1. The section shows distribution of broncho-pneumonic areas (Fig M).

FIG. C 3. Lung of healthy guinea-pig for comparison with Fig. C 2.

FIG. D. Section of lung of guinea-pig shown in Fig. C 1. Extreme congestion with haemorrhage into alveoli and consolidation due to proliferation of alveolar walls. Plugging of bronchioles with desquamated and proliferated epithelium. Proliferation of the endothelial lining of a branch of pulmonary artery towards middle of top of figure. The lymphoid tissue accompanying the vessels and bronchi is a normal feature of the lung of guinea-pig (Fig M 3).

FIG. E. Trachea and bronchi of lung shown in Fig. C 1 (semi-schematic). Accumulation of polymorphonuclear leucocytes in bronchi with blood. The details of congested areas and round-celled infiltration beneath mucous membrane are omitted for the sake of clearness.

FIG. F. Lung of guinea-pig. Old area of consolidation participating in the reaction. Acute congestion, small haemorrhages, active phagocytosis of red cells, proliferation of endothelial cells, excess of eosinophil cells and mononuclear leucocytes, but absence of polymorphonuclear leucocytes, present in upper air-passages (Fig M 3).

FIG. G. Lung of guinea-pig. Details of destruction of alveolar walls and blood-vessels. At top right-hand corner remains of alveolar capillary showing proliferated endothelium, also shown elsewhere throughout figure. Pervasion of walls with fibrin and haemorrhage. Sero-fibrinous exudate in alveoli. Absence of pus.

FIG. H. Liver of guinea-pig showing marked congestion with vacuolation of liver cells.



FIG. J. Kidney of guinea-pig dead 48 hours after intravenous injection of 1 c.c. of subculture of influenza organism. Early acute nephritis. Acute congestion, haemorrhages between tubules. Three glomeruli showing various phases of congestion, proliferation, and occlusion, exudation in one glomerulus. Acute early changes in tubular epithelium.

FIG. K. Rectus abdominis muscle (human). Haemorrhage, infiltration with round cells, and proliferation of sarcolemma nuclei.

FIG. L. Lung of guinea-pig killed 7 days after subdural inoculation of 0.05 c.c. of influenza subculture (4 days' growth). Fibrinous thrombosis of radicles of pulmonary vein. Irregular proliferation of vascular endothelium. Infiltration of adjoining connective tissue and alveolar walls by oedematous (sero-fibrinous) exudate. Normal lymphoid tissue in angle of large and small branches.

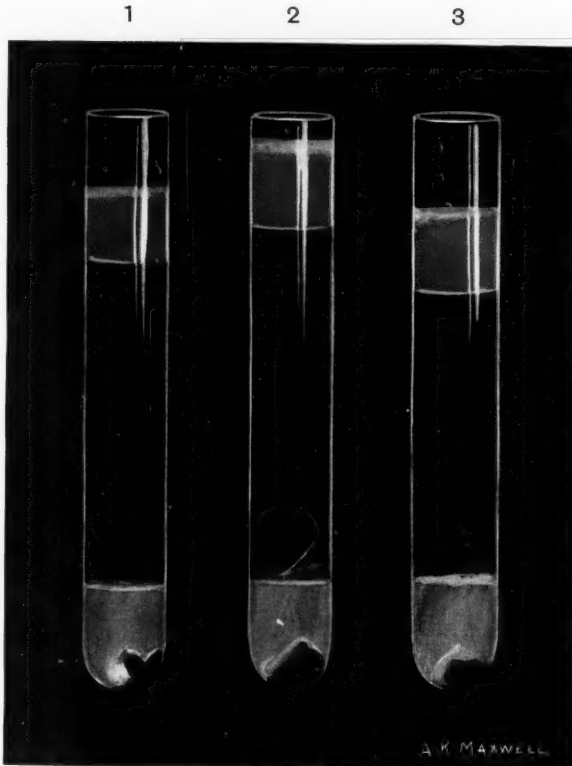


FIG. A. INFLUENZA VIRUS.

- (1) 3 days' growth.
- (2) 5 days' growth.
- (3) 7 days' growth.



2

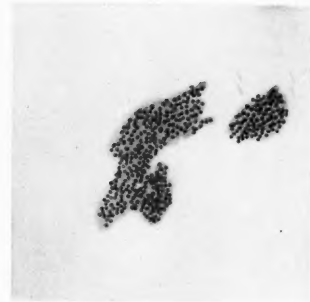


FIG. B. CULTURE FROM SPUTUM.

- 5 days' growth.
- (1)  $\frac{1}{10}$  in. obj. Baker.
- (2)  $\frac{1}{12}$  in. obj. Angus.





FIG. C.





FIG. D.

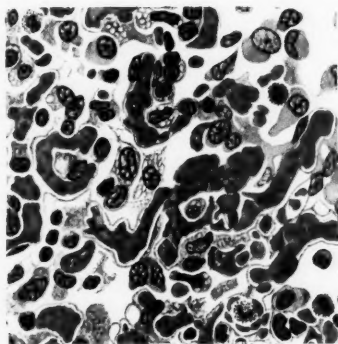


FIG. F.







FIG. E.

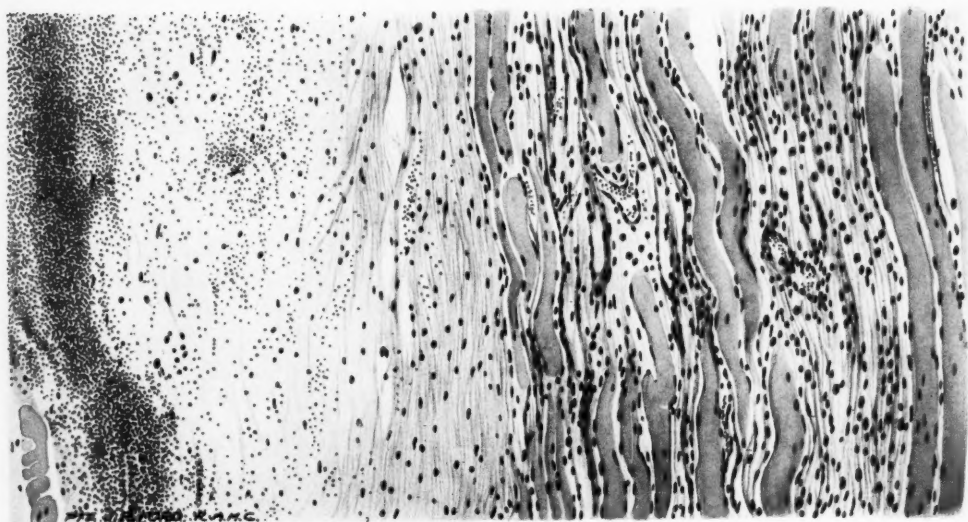


FIG. K.



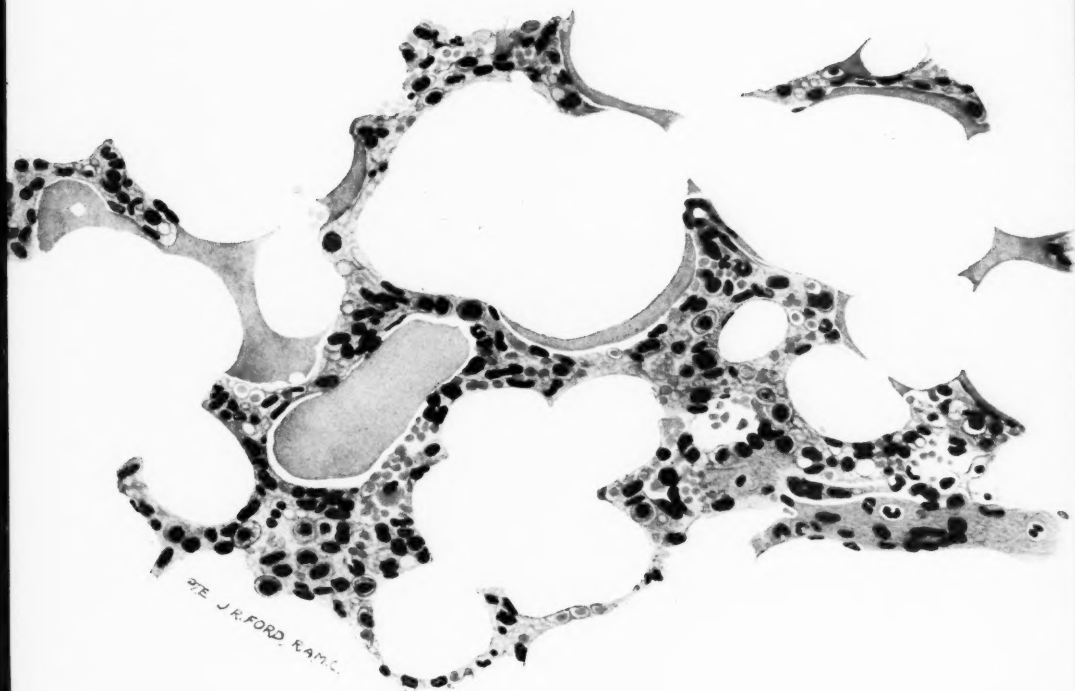


FIG. G.



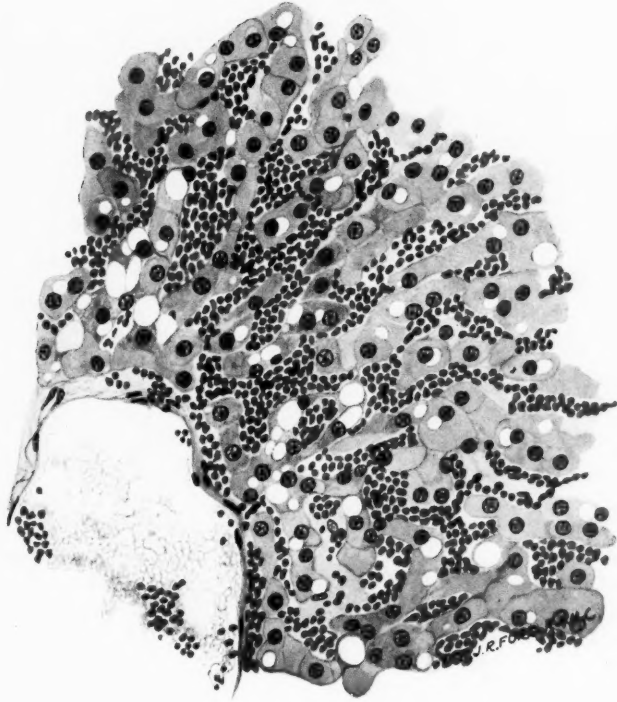


FIG. H.

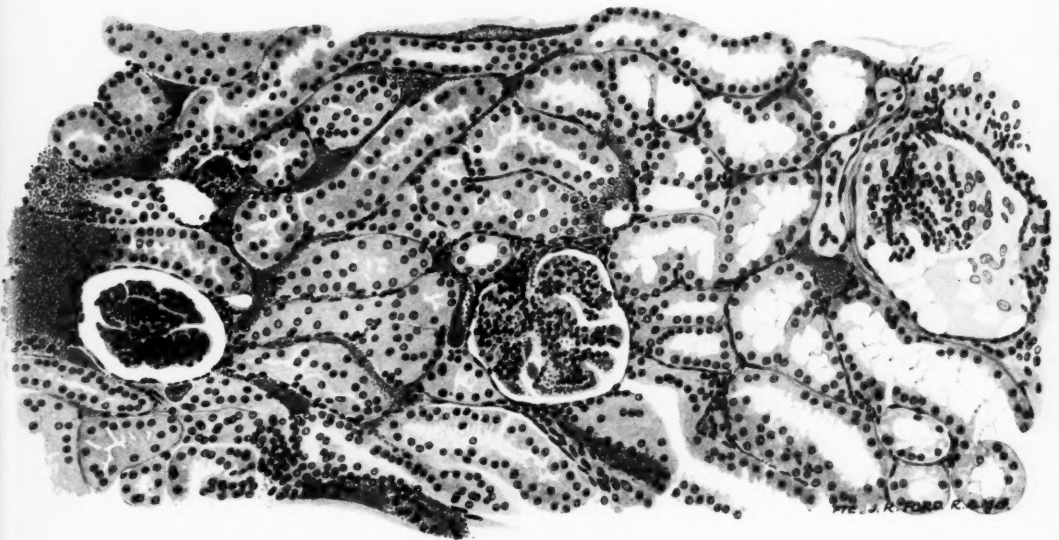


FIG. J.





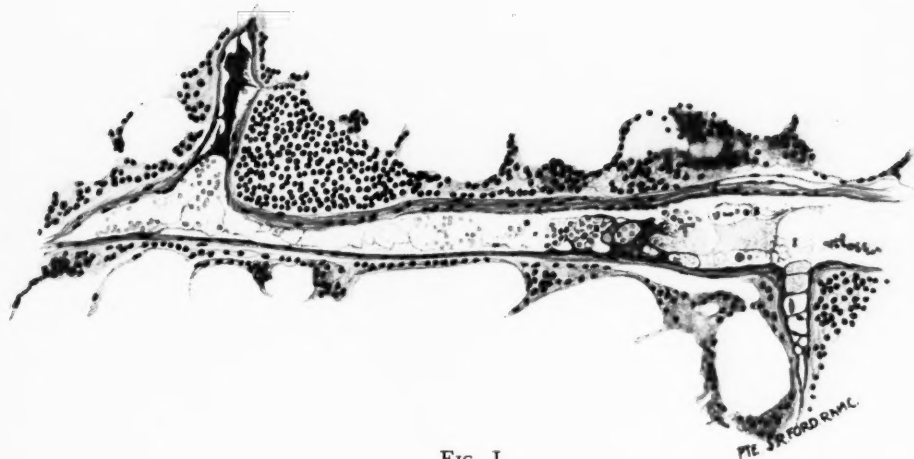


FIG. I.



## A STUDY OF A CASE OF DIABETES MELLITUS TREATED BY THE ALLEN METHOD

BY REGINALD FITZ AND ARLIE V. BOCK

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THE following case of diabetes mellitus is reported to record an observation on the efficacy of the fasting treatment in a case of maximum severity.

*Case history.* J. R. J., belonging to the American Engineers, was admitted to the hospital on June 23, 1918, with the following history. He was a white American soldier, 22 years old, born in North Carolina, and had been in the army about three months. As far as could be made out his family history was negative for diabetes. Several members of his family, however, were said to suffer from 'kidney trouble'.

In 1913 (five years before entry) the patient had an operation for empyema from which he made an uneventful recovery. Except for several other minor operations he had been well in civil life and remembered no serious illness. He had done clerical work. A year previously (1917) he was refused life insurance 'on account of his kidneys' and was advised to avoid 'sweets and acids'. Five months later he reapplied for insurance and was accepted. As soon as he arrived in France (approximately June 3, 1918, three weeks before entry) he developed acutely great thirst, great appetite, and shortly afterwards increasing weakness and polyuria. Since the onset of his illness he had lost, he thought, about three stone in weight. A week before entry (June 16) he reported to his medical officer for these symptoms, and in addition on account of dizziness, headache, and shortness of breath on exertion. A specimen of urine was found to contain sugar and the man was sent to hospital with the diagnosis of diabetes mellitus.

Physical examination showed a well-developed and poorly-nourished individual with marked loss of subcutaneous fat. He seemed stuporous, but could be roused. His breath smelt strongly of acetone, and he was breathing deeply with slight 'air hunger'. His tongue was dry and furred, with throat, tonsils, and teeth not remarkable. The skin was notably dry over the entire body with a tendency to scale.

The chest was flat, with prominent clavicles. The cardiac impulse was in the fifth space nipple line. No enlargement was made out by percussion. The action was regular, not rapid (64), the sounds of good quality, and no murmurs were heard. The blood-pressure was 100 systolic, 80 diastolic. Both chests expanded equally, and were resonant throughout. No areas of consolidation were made out. No râles were heard. An X-ray plate showed no evidence of pulmonary tuberculosis. The abdomen was soft throughout. No masses or areas of tenderness were discovered by palpation. The genitals and reflexes were normal. A casual specimen of urine contained much sugar, a trace of albumin, a heavy ferric chloride reaction, and had a specific gravity of 1.036. The Wassermann reaction was negative.

From this history and these physical findings, the case appeared to be one of acute diabetes with considerable acidosis occurring in a young man without a diabetic family history, without physical or X-ray signs of tuberculosis, and without any evidence of syphilis. It was determined to follow in as much detail as possible the fasting treatment described by Allen (1).

#### *Outline of Treatment.*

According to Allen's views the best-established and most generally accepted theory of diabetes is that it results from deficiency of the internal secretion of the pancreas. As a result there is first a weakened function of carbohydrate metabolism, next a weakened function of protein metabolism, and finally, in severe cases, an imperfect metabolism of fat. For treatment, Allen has turned to experimental diabetes. When about nine-tenths of a dog's pancreas is removed, the resulting condition may appear as a progressively fatal disease. If an attempt is made to keep the dog fat and to satisfy his large appetite, he goes steadily downhill for several months and dies in extreme cachexia. On the other hand, the glycosuria can be stopped by fasting, after which the animal can be placed on a low diet insufficient to cause the reappearance of sugar in the urine, but which will support life almost indefinitely. Such an animal is thin, but strong and lively, with no cachexia and no sign of downward tendency.

Allen's treatment for patients is analogous. The first step is to fast the individual till glycosuria ceases. When the fasting patient has been sugar free for twenty-four or forty-eight hours he is fed cautiously. Usually the first food given after the fast is carbohydrate in the form of green vegetables, and this is increased in regular amounts day by day until a trace of glycosuria appears. The purpose of such a programme is to learn the carbohydrate tolerance and to clear up the last traces of acidosis. After this period protein is added until the patient shows glycosuria or reaches a safe protein ration. Fat is somewhat less urgently needed and can be added as conditions seem to indicate.

In subsequent treatment the attempt to put weight on the patient according to the time-honoured traditions of diabetic treatment is discarded. The most severe diabetic may be thin and weak because he cannot metabolize enough food to be strong or well-nourished, but as long as his weakened pancreas is not overtaxed, and as long as he remains aglycosuric, with a normal blood-sugar concentration, he seems able to retain such weight and strength as he has for at least a considerable period of time. Any attempt to build him up with any kind or quantity of food beyond that which he is able to metabolize perfectly, however, seems to hasten a fatal result. Therefore his diet is restricted to his disease and he is kept sugar free with disregard for his body weight or appearance.

On the whole, the main features wherein the outlined treatment differs from the previously established methods may be summarized under three headings. The first two represent differences merely of degree, in that the treatment is more radical than the old; namely, first an initial fast sufficient to clear up glycosuria in any case and usually one or two days longer; second, a subsequent diet to keep glycosuria and acidosis permanently absent, with as many interspersed fast-days as may be necessary for this purpose. The third feature represents differences not in degree but in kind, and is diametrically opposed to the prevalent teachings; it opposes the idea that the diabetic should be kept at the highest possible level of weight and strength and that gain in weight is synonymous with improvement; it substitutes for this the plan of keeping the severest diabetics intentionally and permanently at a sufficiently low level of weight and metabolism in the belief that return of symptoms and downward progress is thus prevented. Whatever the ultimate outcome of a given case, two conclusions seem justified by present knowledge. The treatment removes glycosuria and acidosis

more quickly and surely than has been the practice heretofore, and patients do better when glycosuria and acidosis are removed than when they are allowed to continue.

#### *Details of Treatment.*

In the present case, the above outline of treatment was followed conscientiously. At entry the patient was put to bed, giving an enema and a dose of castor oil. He was then fasted for seven days, or until he was aglycosuric for twenty-four hours, without further medication. During this time he was encouraged to drink plenty of water, was given weak tea three times a day without milk or sugar, and was allowed 1,000 c.c. of thin soup a day made from one Oxo cube. After the urine was sugar free for twenty-four hours, the patient's carbohydrate tolerance was tested by vegetables, and finally a mixed diet well within the limits of tolerance was constructed to contain enough protein to satisfy protein destruction, enough carbohydrate to prevent the development of any serious acidosis, and enough calories of food to maintain reasonable comfort. Such a course, to be without danger, demanded careful laboratory work by accurate methods so that the data obtained were reliable, and by sufficiently simple methods so that they could be carried out in a hospital such as the one existing.

A diet kitchen was established in charge of one Sister who was given exclusive care of the case. The necessary equipment consisted in a pair of scales weighing to half a gramme, a measuring cylinder, weighing dishes, and a standard table of food analyses such as Atwater and Bryant's (2).

Being summer, it was possible to buy a variety of fresh vegetables at slight expense. The Sister went to market each day and bought vegetables for the day following. Their carbohydrate, protein, and fat content were estimated from food tables, the quantities necessary for any specified diet were worked out by arithmetic, tabulated, and subsequently weighed and cooked. In this way a 'prescription diet' was ordered and accurately filled each day without undue labour or expense. The fast was broken with 10 gm. of carbohydrate, and 10 gm. were added to this initial diet each day.

Finally the patient was able to tolerate 150 gm. of carbohydrate without glycosuria. To make this diet, 315 gm. of tomatoes, 382 gm. of asparagus, 100 gm. of cauliflower, 150 gm. of cucumber, 150 gm. of spinach, 256 gm. of string beans, 112 gm. of potato, and 19 gm. of bread were used, making in all a total of 2,684 gm. of bulk. The patient ate this large amount willingly.

By this time all benefit which could be derived from a nearly pure carbohydrate diet seemed gained, and the patient was given a mixed diet containing 75 gm. of protein, 50 gm. of carbohydrate, and 1,750 calories. This diet was made from 400 gm. of tomatoes a day, 300 gm. of asparagus, 100 gm. of cabbage, 177 gm. of spinach, 55 gm. of potato, 128 gm. of cucumber, 4 eggs, 100 gm. of lamb, 97 gm. of bacon, 15 c.c. of olive oil, and 18.5 gm. of butter. The patient was kept on this for a week, gaining strength rapidly, excreting no sugar, and with normal blood-sugar concentration. He was then evacuated after a total of thirty-three days of observation.

Certain laboratory facts were essential to follow the patient's progress. It was necessary to determine the amount of sugar excreted during the period of glycosuria and to discover the least possible recurrence. It was important to estimate the blood-sugar concentration from time to time as maximum tolerance is not obtained and improvement does not usually occur while the blood-sugar is appreciably above normal. Since fasting was undertaken to remove acidosis as well as glycosuria this phase of the disease was studied. Finally the case showed remarkable disturbances in protein metabolism, and thus an index of nitrogen excretion was of clinical significance.



The various methods employed were simple, accurate, and required few special laboratory instruments or reagents. The urine was collected in wide-necked glass bottles by the patient himself, and was separated into four specimens each day, the first containing the urine excreted between seven in the morning and twelve noon, the second from twelve noon until seven in the evening, the third from seven in the evening until midnight, and the fourth from midnight until seven in the morning. This was done to detect traces of sugar. On two occasions a questionable trace, which was missed in a mixed specimen, appeared in one of the four specimens. It was important to detect such a trace as it was proposed to keep the patient's urine absolutely sugar free.

The specimens were measured and tested for sugar separately by Benedict's (3) qualitative test. The total twenty-four hour urine was recorded and a mixed specimen obtained for further analysis. As a routine, the specific gravity was estimated, the sugar, when present, by fermentation, aceto-acetic acid qualitatively by the ferric chloride reaction, and the urea and ammonia nitrogen by the method of Van Slyke and Cullen (4). Thus, from such simple urinalysis, sugar excretion was followed, nitrogen excretion was indicated by the accurate determination of the urea and ammonia nitrogen which represents between 80 and 90 per cent. of the total, acetone body excretion was studied qualitatively by the ferric chloride test and more quantitatively by the excretion of ammonia. The patient was bled frequently with a fine needle for observation on blood-sugar and acidosis. The blood was oxalated to prevent clotting, centrifugalized, and the plasma used for analysis. The plasma sugar was estimated by the colorimetric method of Meyers and Bailey (5). The combining power of the plasma for  $\text{CO}_2$  was used to determine the degree of acidosis and was found by Van Slyke's (6) method. For convenience, this finding was translated into the corresponding  $\text{CO}_2$  tension of the alveolar air—an estimation which Beddard, Pembrey, and Spriggs (7) have found of great importance in the prognosis of diabetic acidosis. The influence of fasting, of a carbohydrate diet, and of a mixed diet upon the case is shown by the following tables.

*The Effect of Fasting on Glycosuria and Glycaemia.*

The effect of the fast on the urinary sugar and blood-sugar is shown in Table I.

TABLE I.

Day.	Urine Amount.	Specific Gravity.	Sugar.	Blood-Sugar.
	c.c.		Grm.	%
1	2400	1034	116.0	0.58
2	1600	1035	77.3	0.27
3	2450	1023	67.2	0.27
4	3200	1014	51.5	0.27
5	2700	1012	24.9	0.25
6	3850	1007	Traces	0.24
7	3650	1006	None	0.17

As can be seen, the excretion of sugar diminished day by day as the fast continued, dropping rapidly at the beginning and end. The blood-sugar curve is more striking and demonstrates the importance of the determination. On the first day it was high and dropped suddenly. Then for five days it remained practically constant. When the patient became sugar free it was still 0.17 per cent., which is nearly double the normal. Had the patient been fed immediately upon even a low mixed diet, it is almost a certainty that he would have excreted sugar and would have had to fast again. As it was, he was given 10 gm. of carbohydrate and 60 calories, which was essentially another fast-day. This had

a beneficial moral effect upon the patient, as he knew he might expect an increase on the following day, and gave the blood-sugar a chance to become more nearly normal.

*The Effect of Fasting on Acidosis and Acid Excretion.*

This is shown in Table II.

TABLE II.

Day.	Urine Amount.	Specific Gravity.	Ammonia Nitrogen.	Ammonia Nitrogen		Ferric Chloride Reaction.	Alveolar CO <sub>2</sub> Tension.
	c.c.		gram.	Ammonia Nitrogen and Urea Nitrogen.	%		mm.
1	2400	1034	6.98		37.4	+++	20.0
2	1600	1035	2.94		20.4	+++	22.8
3	2450	1023	3.26		17.5	++	32.4
4	3200	1014	2.49		15.4	+	42.0
5	2700	1012	1.88		13.3	+	44.2
6	3850	1007	1.82		11.7	Trace	44.8
7	3650	1006	1.37		8.3	Trace	

Here, again, the effect of fasting was very striking. At entry the alveolar CO<sub>2</sub> tension was 20 mm., a point close to the danger mark. With fasting it rose steadily, so that on the fourth day it was within normal limits, and there was no longer a question of death by coma. During the first twenty-four hours nearly 7 gm. of ammonia nitrogen was excreted. This dropped consistently to 1.37 gm. on the last fast-day. The ratio between the ammonia nitrogen and the ammonia and urea nitrogen was equally improved. At first the ammonia represented 37 per cent. of the nitrogen so estimated, but fell by fasting to 8 per cent. six days later.

The two foregoing tables demonstrate that the patient at entry had a high blood-sugar concentration, was excreting a large amount of sugar, had developed a serious degree of acidosis, and was excreting large amounts of acetone bodies as indicated by ammonia excretion. As final proof of the severity of the case, the nitrogen excretion during the fast is offered. This is shown in Table III.

*The Effect of Fasting on Nitrogen Excretion in relation to Sugar Excretion.*

TABLE III.

Day.	Urine Amount.	Specific Gravity.	Sugar.	Nitrogen.*		D = N Ratio.
	c.c.		Grm.	Grm.	Grm.	
1	2400	1034	116.0	19.25	6.02 = 1	
2	1600	1035	77.3	17.32	4.45 = 1	
3	2450	1023	67.2	18.40	3.65 = 1	
4	3200	1014	51.5	19.38	2.66 = 1	
5	2700	1012	24.9	18.62	1.33 = 1	
6	3850	1007	Traces	18.60		
7	3650	1006	None	19.72		

\* This is estimated from the urea and ammonia nitrogen, which together were assumed to represent 83 per cent. of the total nitrogen.

While the data in the foregoing table are not absolutely correct, nevertheless certain justifiable and interesting conclusions may be drawn. In the first

place, the diabetes had progressed sufficiently to upset protein metabolism to a marked degree. It is difficult to explain the large amount of nitrogen excreted at the end of a seven-day fast in any other way. Secondly, the  $D = N$  ratio on the third day of the fast was approximately  $3.65 = 1$ . It is reasonable to believe from this evidence that, even after three days of fasting, the case was still extremely severe and almost, if not entirely, a 'total diabetic'.

The subsequent progress of the case was as follows :

*The Effect of Increasing Amounts of Carbohydrate and of a Mixed Diet upon Glycosuria and Glycaemia.*

TABLE IV.

Day.	Protein.	Fat.	Carbo- hydrate.	Calories.	Urine Amount.	Specific Gravity.	Sugar.	Blood- Sugar.
					c.c.		gram.	%
6		Fasting			3850	1007	Trace	0.24
8	2.9	1.0	10	61	2875	1006	0	0.17
12	21.6	5.1	50	341	3870	1005	0	0.09
15	30.4	7.8	80	525	4630	1006	0	0.10
18	39.0	9.5	100	658	3925	1009	0	0.08
24	44.2	12.5	150	911	5250	1008	0	0.10
27	75.0	132.7	50	1750	2900	1012	0	0.08
33	75.0	132.7	50	1750	2220	1018	0	0.07

The urine remained consistently free from sugar. The blood-sugar on the carbohydrate diet continued to fall, and after reaching normal remained within normal limits despite the change in diet at the end. On the twenty-fourth day, when the patient was receiving 150 gram. carbohydrate, a more careful test was made in regard to the effect of so much food upon the blood-sugar. The patient was bled before breakfast and two hours and a half after each meal, when the post-absorptive hyperglycaemia might be expected to have reached its highest figure. The result of this test is shown in Table V.

TABLE V.

Time.	Protein.	Fat.	Carbohydrate.	Calories.	Blood-Sugar %.	Urine.
7 a.m.					0.10	Sugar test negative in all four speci- mens for the 24 hours of that day
8 a.m.	14.1	3.8	45.0	278		
10.30 a.m.					0.12	
12.00 noon	16.0	5.0	52.5	326		
2.30 p.m.					0.09	
5.00 p.m.	14.1	3.7	52.5	307		
7.30 p.m.					0.12	
Total	44.2	12.5	150.0	911		

There was a slight rise in blood-sugar after breakfast and supper, but so insignificant as to justify the belief that the patient was still well within his tolerance.

*The Effect of Increasing Amounts of Carbohydrate and of a Mixed Diet upon Acidosis and Acid Excretion.*

TABLE VI.

Day.	Protein.	Fat.	Carbo- hydrate.	Calories.	Urine Amount.	Specific Gravity.	Ammonia Nitrogen.	Ammonia Nitrogen	Ferric Chloride Reaction.	Alveolar CO <sub>2</sub> Tension.
								Ammonia Nitrogen and Urea Nitrogen.		
					c.c.		gram.	%		mm.
6	Fast				3850	1007	1.82	11.7	Trace	44.8
8	2.9	1.0	10	61	2875	1006	1.12	9.7	Neg.	51.0
12	21.6	5.1	50	341	3870	1005	0.49	7.7	Neg.	53.8
15	30.4	7.8	80	525	4630	1006	0.50	6.3	Neg.	49.6
18	39.0	9.5	100	658	3925	1009	0.26	3.6	Neg.	
24	44.2	12.5	150	911	5250	1008	0.32	3.4	Neg.	53.8
27	75.0	132.7	50	1750	2900	1012	0.39	3.9	Neg.	47.6
33	75.0	132.7	50	1750	2220	1018	0.71	5.7	Neg.	45.5

As might be foreseen, the ammonia nitrogen excretion dropped quickly with a carbohydrate diet to about 0.30 gram. in twenty-four hours. At the same time the ratio between ammonia nitrogen and ammonia plus urea nitrogen fell to about 4 per cent. The ferric chloride reaction disappeared and remained negative. The alveolar CO<sub>2</sub> tension rose, proving that all acidosis had cleared up. When the carbohydrate was cut down, and the fat markedly increased, there was an immediate slight but definite acidosis. The alveolar CO<sub>2</sub> tension fell from 53.8 mm. to 45.5, the ammonia nitrogen rose to 0.71 gram., and the ammonia nitrogen ratio increased to 5.7 per cent. If it had not been necessary to evacuate the case, even such a mild reaction could have been overcome by further manipulation of the diet. The diet seemed safe, however, from this observation and that of the blood-sugar, and nothing further was attempted.

*The Effect of Increasing Amounts of Carbohydrate and of a Mixed Diet upon Nitrogen Excretion.*

TABLE VII.

Day.	Protein.	Fat.	Carbo- hydrate.	Calories.	Urine Amount.	Specific Gravity.	Nitrogen.*
					c.c.		gram.
6	Fasting				3850	1007	18.60
8	2.9	1.0	10	61	2875	1006	14.50
12	21.6	5.1	50	341	3870	1005	7.56
15	30.4	7.8	80	525	4630	1006	9.66
18	39.0	9.5	100	658	3925	1009	8.76
24	44.2	12.5	150	911	5250	1008	11.31
27	75.0	132.7	50	1750	2900	1012	12.10
33	75.0	132.7	50	1750	2220	1018	15.12

\* This is estimated from the urea and ammonia nitrogen, which together were assumed to represent 88 per cent. of the total nitrogen.

Here the sparing effect of carbohydrate upon protein metabolism is well illustrated. As soon as the fast was broken, the nitrogen excretion diminished strikingly. As the carbohydrate diet increased, and with it the protein intake

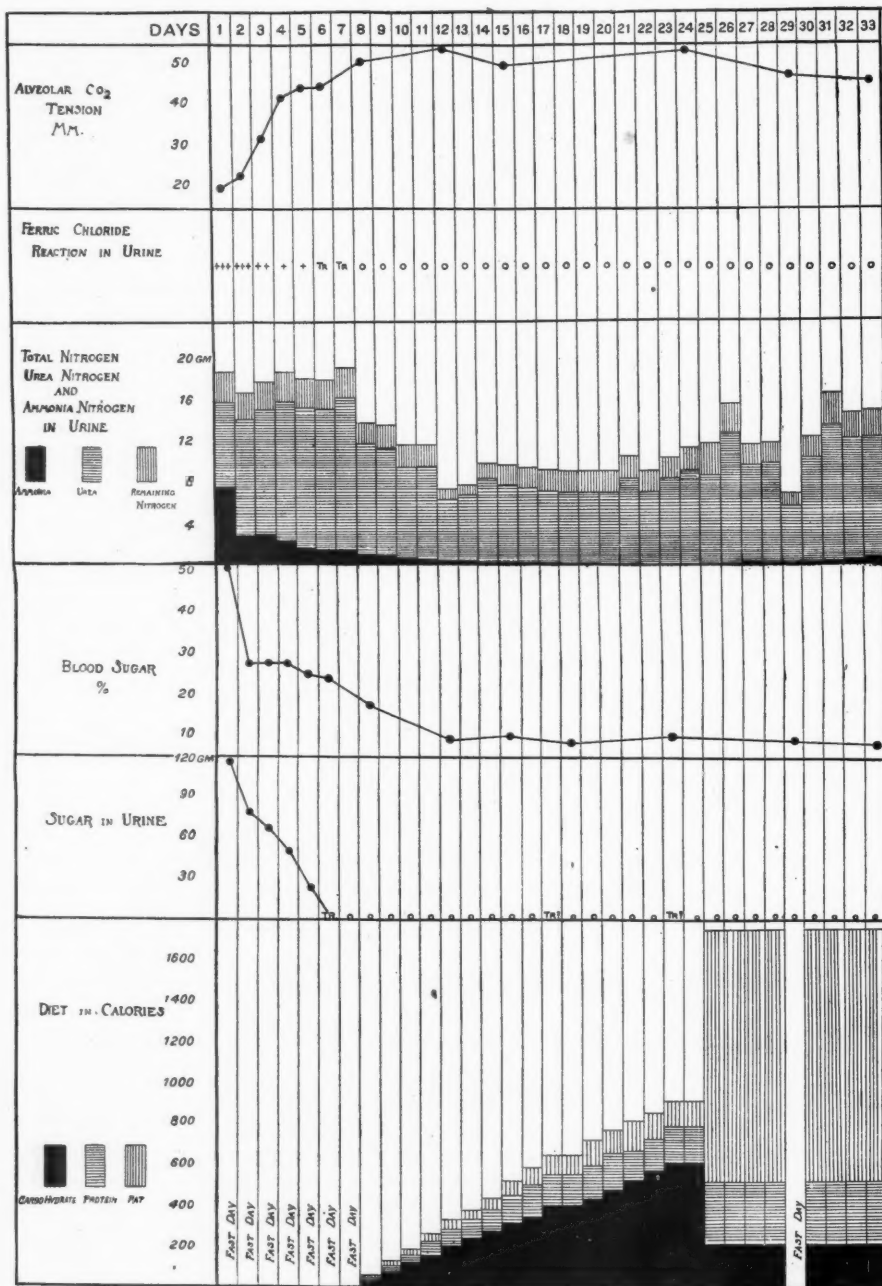


CHART.\*

\* The total nitrogen is estimated from the urea and the ammonia nitrogen, which together were assumed to represent 83 per cent. of the total.

to a certain extent, nitrogen excretion rose. On the last day, the patient excreted approximately 15 gm. of nitrogen upon a diet theoretically containing 12 gm. Whether this observation is absolutely true or not, it is a sufficiently marked change. After fasting seven days there was still a nitrogen loss of about 19.0 gm. per twenty-four hours, or of about 120 gm. of body protein. After his course of treatment the patient was discharged in a condition approaching nitrogen equilibrium. A graphic chart of the daily observations upon the case is added to show whatever findings have not been recorded in the tables.

### *Summary.*

This paper reports observations upon a case of diabetes mellitus. At entry to hospital the patient had a blood-sugar concentration of 0.58 per cent. and an acidosis sufficient to lower his alveolar  $\text{CO}_2$  tension to 20 mm. During the first twenty-four hours in hospital he excreted 116 gm. of glucose and 6.98 gm. of ammonia nitrogen. These facts show that the patient was critically ill. On the third day of a carbohydrate-free diet the patient's urine showed a  $\text{D} = \text{N}$  ratio of approximately  $3.65 = 1$ , and afforded additional evidence that the case was one of maximum severity. The patient was treated according to the method proposed by Allen, and illustrates its value in a favourable case. A seven days' fast was necessary to render the patient's urine free from sugar. At the end of this period the blood-sugar had fallen to 0.17 per cent., the alveolar  $\text{CO}_2$  tension had risen to 44.8 mm., the ammonia nitrogen excretion had fallen to 1.37 gm., and the patient's condition was much improved.

After the urine was sugar free, the carbohydrate tolerance was tested by a systematic daily increase in as pure a carbohydrate diet as was possible to be obtained in the form of green vegetables. The patient tolerated 150 gm. of carbohydrate by this method without becoming glycosuric. During this time the blood-sugar fell to normal, and was not found materially increased on the last day of the test, when repeated bleedings were made to determine the degree of post-absorptive hyperglycaemia. During the period of carbohydrate feeding, the alveolar  $\text{CO}_2$  tension remained high, and the ammonia nitrogen excretion dropped to about 0.30 gm. in twenty-four hours, showing that all acidosis had disappeared. The carbohydrate-sparing effect on protein metabolism was demonstrated. The nitrogen excretion dropped from about 19 gm. in twenty-four hours on the last day of the fast, to about 7.5 gm. when protein intake was low. As the vegetable protein intake increased considerably the urinary nitrogen increased somewhat.

After thirty-three days' observation the patient was discharged from hospital in good condition with normal blood-sugar concentration, with trivial acidosis, and approximately in nitrogen equilibrium upon a mixed diet within his tolerance, yet ample for his bodily needs.



## REFERENCES.

1. Allen, *Boston Medical and Surgical Journal*, 1915, clxxii. 241; *American Journal of Medical Science*, 1915, cl. 480; *ibid.*, 1917, cliii. 313.
2. Atwater and Bryant, *United States Department of Agriculture*, 1906, Bulletin 28.
3. Benedict, *Journal American Medical Association*, 1911, 1193.
4. Van Slyke and Cullen, *Journal Biological Chemistry*, 1914, xix. 211.
5. Meyers and Bailey, *ibid.*, 1916, xxiv. 149.
6. Van Slyke, *ibid.*, 1917, xxx. 347.
7. Beddard, Pembrey, and Spriggs, *Lancet*, 1903, i. 1366.

## LYMPHOCYTOSIS IN SOLDIERS

### A CLINICAL AND HAEMATOLOGICAL STUDY

By JOHN B. McDOUGALL

#### *Introduction.*

WHATEVER the explanation of the phenomenon may be, it appears to be definitely established that there is a marked change from normal in the relative number of white cells in the blood in certain diseases peculiar to active service. This haematological diversion is not to be wondered at when one considers that so many of the ordinary medical diseases, or rather diseases which were originally considered to be commonplace in clinical medicine, have now been placed beyond the province of pre-war medicine, and have amassed for themselves a literature bristling with new discoveries and new theories. The typical pre-war nephritis is modified now to a nephritis with specific limitations, and the familiar picture of acute Bright's disease, so common in civil hospitals, is a comparatively rare one in the hospitals in France.

Similarly, acute rheumatic fever forms a strikingly small percentage of our medical cases, as do also the cases of malignant endocarditis and, say, enteric fever.

In place of these more or less well-known pre-war diseases, we have been introduced to a group of ailments of a chronic type, most of them non-fatal in their end results, but, nevertheless, powerful in their mode of action, and far-reaching in their toll of sufferers.

The new terminology would classify many of these diseases as trench feet, trench nephritis, P. U. O., trench fever, and D. A. H., but the object of this paper is to direct attention to the blood changes which are characteristic of one or two of those conditions, and to endeavour to show that the new terminology has at least some measure of haematological evidence to support it.

The object of the work in hand was to discover, if possible, (1) whether there was any total or differential count of the white cells which could be taken as characteristic of any of the types of trench fever met with clinically; (2) the incidence of tachycardia (D. A. H.) as a true sequel of trench fever, and the blood condition in these cases; (3) other conditions met with in active service showing similar blood changes. The method employed in estimating the total number of cells was the usual one, the Thoma-Zeiss haemocytometer

being the instrument employed. For the differential counts, two films at least were taken from every case, and the better one chosen and stained for enumeration of the cells. Owing to the admirable nuclear staining given by Leishman's stain, that one alone was used. Three hundred cells were counted on each film, but in some cases, where the count showed evidences of being markedly divergent, four hundred cells were classified. In the actual classification of the cells, the basophil leucocytes were grouped with the polymorphonuclear leucocytes. In none of the films examined did they amount to 1 per cent. of the total number of white cells. Although there is much to be said against classifying the mononuclear cells into lymphocytes and large mononuclears, I offer no excuse for so doing on this occasion.

No special enumeration was made of degenerated forms, of 'leucocytoid' types, or of mesolymphocytes, since these are generally recognized to be of the same origin, type, and significance; these were all classed as lymphocytes. The so-called Rieder cell was also included in the lymphocyte series.

Similarly, in the large mononuclear group are included large hyaline cells and transitionals, since these have probably everything in common except their stage of development.

At the outset of the investigation I was fortunate in having the co-operation of Capt. W. Templeton, Pathologist, No. 47 General Hospital, who helped me with the haematology in 70 cases.

Since November 1917, I have been working in conjunction with Major Anthonisz, Assistant Advisor in Pathology to Calais Area; he has been good enough to corroborate my findings in many cases, besides giving me every facility for working in the laboratory under his command.

From the pathological side, then, the work has had the advantage of having been attacked by three different observers, an important point in eliminating the personal equation.

From the clinical aspect, however, I have worked more or less independently, but at the same time I owe a debt of gratitude to Major J. R. Collins, officer in charge, Medical Division, No. 30 General Hospital, for allowing me to collect the cases in wards under my supervision. Careful clinical notes have been taken from day to day, and charts illustrating the temperature and pulse-rate curves have been made in all cases.

#### *The Total and Differential Count of the White Cells in Types of Trench Fever.*

The primary difficulty was to classify the clinical types of trench fever. For obvious reasons the subjective symptoms were useless for this purpose; the usual syndrome of pains in the head, back, especially the lower lumbar region, and in the shins, was more or less peculiar to all cases of trench fever.

Similarly, objective symptoms gave no better opportunity for classification purposes, as in many cases these were nil. Splenic enlargement to the palpable state was found in two cases in the entire series, and the urinary examination was negative in so many, that no effort was made to identify a type or class from the findings of either splenic percussion or of the urinary examination.

The one sign which was found sufficiently frequently to entitle it to pre-eminence in the separation of the cases was acceleration of the pulse-rate, the so-called D. A. H. Accordingly I have separated these cases showing definite cardiac instability from the others, but, at the same time, an effort has been made to state precisely, where possible, the type of trench fever which preceded or accompanied the disordered action of the heart.

From the temperature chart the most valuable information is to be obtained, and there is no valid reason for departing from the classification suggested by the Committee appointed to investigate P. U. O. They based their report on an analysis of 170 cases, and elaborated three types, differing from each other chiefly in the course of the pyrexia, viz.:

Type A. (1) Regularly relapsing cases (56 cases, or 32.9 per cent.).

(2) Irregularly relapsing cases (35 cases, or 20.5 per cent.).

Type B. (1) Cases beginning with a single short bout of fever lasting under six days.

(2) Cases which did not give any history of elevation of temperature prior to the time of observation, and which did not have relapses of fever whilst under observation.

27 cases, or 15.8 per cent., were included under Type B.

Type C. Cases with a definite and prolonged initial period of fever, resembling that found in the enteric group of infections (52 cases, or 30.5 per cent.).

It is important to note that the irregularly relapsing cases include those in which 'the intervals between the relapses are not so definite, or if the intervals are definite, the temperature remains above the normal'. My own results are based on a study of 200 cases of trench fever, collected over a period of twelve months.

The proportion of cases falling under the groups considered above are as follows:

Type A. (1) Regularly relapsing cases (56, or 28 per cent.).

(2) Irregularly relapsing cases (109, or 54.5 per cent.).

Type B. 22 cases, or 11 per cent.

Type C. 13 cases, or 6.5 per cent.

In comparing the two series of observations, it is interesting to note that Type A (1) is to be found in approximately the same percentages. The reason

for the preponderance of Type A (2) in my series, and for the paucity in the numbers of those included in Types B and C, I shall endeavour to explain below.

*The Characteristics of the Total and Differential White Cell Count in Type A (1), i.e. the Regularly Relapsing Type.*

The regularly relapsing type of trench fever is the one to which most attention has been given so far; it is definite, inasmuch as it has, as the name suggests, a relapse of fever at intervals.

These intervals, however, are not definite in themselves. The clinical manifestations accompanying this type of fever have been described frequently. In all, 74 total counts have been made, and the general tendency has been towards a leucocytosis. The highest count in the series was 24,600 per c.mm., the lowest 5,625.

The average total count taken during the pyrexial stage of the disease cannot be contrasted with the average total count during the apyrexial stage, for each case would seem to have its own 'mean'.

A patient with a count of 12,500 cells per c.mm. and a temperature of 98.8° F. had 19,000 cells when the temperature was 100° F.

On the other hand, a man who had 16,000 per c.mm. during the apyrexial stage gave only 15,987 when the temperature reached 101.4° F. Average counts, therefore, cannot be relied upon; it would appear rather that each case has its own average.

As a general rule, however, it may be said that the total count during the fever is in excess of the total count during apyrexia—in some cases this is marked, but it is not a change of any definite clinical value.

The most characteristic change takes place during the periods of pyrexia. Briefly, there is a relative increase in the polymorphs, and a diminution in the number of lymphocytes during the fever; this is a typical and constant feature in the white cell count.

Ninety-one differential blood-counts have been made in the 56 cases coming under Type A (1), and with most interesting results.

As with the total count, the degree of polymorphonuclear leucocytosis is not always proportionate to the rise of the temperature, but it always occurs during the fever, and at the expense of the lymphocytes, which may fall to 15 or 20 per cent. after forming anything from 30 to 60 per cent. of the total number of white cells during the apyrexial stage. This change is most marked when the temperature has been steadily subnormal in the intervals between the paroxysms of fever. I have records of cases where the polymorphs have increased as much as 27 per cent. and lymphocytes have fallen 28.2 per cent. in a few hours, during which the temperature has risen from 98° to 103° F. This reciprocal fluctuation must be marked out as extremely characteristic of the relapsing type of trench fever. In cases of this type where two or more counts

were made at intervals during the various phases of the disease, 100 per cent. of the cases showed this phenomenon.

There is only one difficulty, and that presents itself when the pyrexial paroxysms are only slight, say to 98.8° or to 99° F.

I have found in these cases, more particularly towards the end of the period of observation of the patient, there may be some difficulty in interpreting the result, for with a temperature of 99° F. the differential count is not always dislocated towards the polymorph end. In this respect it calls for comment, for many of the cases of Type A (1) merge gradually into Type A (2), where, as is stated below, much less accuracy can be obtained. Nevertheless, there have been cases in this series where the changes described above have been well marked when the temperature was not more than 99° F.; but it has also been noted that there is no tendency in these men for the type to be changed, the temperature of 99° F. being merely 'a reminder' that the relapses have not entirely disappeared.

Occasionally one meets with a more or less normal differential count after a long period of pyrexia of the relapsing type. Clinically such patients are well; they do not complain of the head, back, or shin pains, and there is no tachycardia, although they are sometimes weak and easily tired. It is perhaps too much to assume that such patients, showing no lymphocyte excess, are free from infection, but the absence of subjective symptoms, plus a normal temperature, pulse-rate, and differential leucocyte count, is a good passport to convalescence at least. Conversely, there are cases in this particular group which have showed constant lymphocytosis in the presence of a normal temperature, after having had typical periodic bouts of fever.

Symptoms of pain have never been absent in such cases, more especially the shin pains. The response to effort as measured by the pulse-rate is not good, although the pulse-rate at rest may be within normal limits. The following counts are taken from the record of a patient who was admitted to hospital with symptoms of regularly relapsing fever. The blood was examined on five different occasions when the temperature was normal. This patient was never free from pains in the legs, and as 'convalescence' proceeded a fine tremor developed in the hands. The pulse-rate was normal when he was at rest, but the slightest exercise brought about a pronounced tachycardia.

*Blood Examination:*

Date.	Total.	Polys.	Eosinos.	Lymphs.	Large Monos.	Temp.
9.2.18	14,000	37.7	1.3	54.0	7.0	98.2° F.
25.2.18	15,980	41.0	1.7	47.8	9.5	98.6° F.
1.3.18	10,980	40.0	1.3	54.8	3.9	97.8° F.
6.3.18	11,250	34.6	1.6	57.5	6.3	98.2° F.
14.3.18	15,980	45.0	1.3	40.6	13.1	98.2° F.

Microscopically, the cells show nothing abnormal. They take the stain well, and no intracellular organisms have ever been noted. Azurophil granules have been well marked in many cases, but that feature is dependent more upon



the technique of the staining of the films, than upon any inherent quality in the cells themselves. Blood platelets are apparently not increased in number or size.

This sudden and abrupt change from relative and absolute lymphocytosis during apyrexia to polymorphonuclear leucocytosis during pyrexia is interesting from the theoretical point of view. From an analogy with malaria, when a practically similar phenomenon takes place, it would appear to indicate that there is a definite cycle of the organism in the system. At the time of the pyrexia there is an exacerbation of the symptoms; the pains become more severe, the pulse is accelerated in proportion to the elevation of the temperature, and the skin is hot and frequently bathed in perspiration. It is true the successive bouts of temperature are usually less in magnitude, and this would also indicate an immunizing process being at work, but whether the polymorphs are the agents for determining the immunization during the fever, or whether it is the lymphocytes during the non-febrile period, cannot be answered. So far, no immune bodies have been discovered in the plasma, but the similarity of the course of the fever to that of patients with pulmonary tuberculosis undergoing a series of auto-inoculations by graduated exercise is suggestive, although the degree of lymphocytosis in apyrexia phthisis is not nearly so well marked as in cases of trench fever.

Until immune bodies have been found in the blood of patients suffering from trench fever, it would be well to bear in mind the cellular theory of immunization. In none of my cases was there any evidence of appreciable enlargement of the inguinal or other lymphatic glands, such as is met with in certain other conditions where a lymphocytosis is characteristic of the blood picture.

*The Characteristics of the Total and Differential White Cell Count  
in Type A (2), i. e. the Irregularly Relapsing Type.*

The cases of irregularly relapsing fever have constituted by far the largest number in my series—109, or 54.5 per cent.

The reason of preponderance of Type A (2) cases is due, in part at least, to the fact that the temperature charts have revealed the presence of slight and irregular elevations of temperature in cases which have been under observation for three or four weeks, and which were at the outset considered to belong to Type A (1) or even to Type B.

I am of the opinion that many cases of regularly relapsing fever do actually pass into the irregular form as time goes on, and that the type at present under consideration represents the more chronic form of trench fever, as well as the one which is least of all amenable to treatment. The patient is constantly complaining of aches and pains; the night hours are a continual source of worry to him. He has no period of comparative well-being such as is enjoyed by the patient with the regularly relapsing form during the

apyrexial period of the disease. Ninety-four total counts have been made in cases belonging to this category, and what has been said about the total count in Type A (1) applies with equal force to this series. Ten to fourteen thousand white cells per c.mm. is a very common figure with a normal temperature, but here again each case would appear to have its own 'mean'. In one case in particular, six total counts at different intervals gave the following results:

- |                             |                            |                              |
|-----------------------------|----------------------------|------------------------------|
| (1) 18,125 (temp. 101° F.). | (3) 19,400 (temp. 97° F.). | (5) 17,600 (temp. 98.2° F.). |
| (2) 18,125 (temp. 100° F.). | (4) 17,200 (temp. 99° F.). | (6) 18,600 (temp. 98.4° F.). |

No direct inference can be obtained from such figures as these, but it has been noted on several occasions in this class of case, that the general tendency is for the total count to bear a fairly close relationship to the intensity of the subjective symptoms. In the case quoted above the leg pains were exquisitely severe.

The outstanding feature of the analysis of the 116 differential counts in the irregularly relapsing form of trench fever is undoubtedly the large percentage of cases showing mononuclear excess. The fluctuation from lymphocytosis to polymorphonuclear leucocytosis, so characteristic of Type A (1), is not to be found here to anything approaching to the same extent. Of course it is to be remembered that the outstanding feature of these cases is the irregular temperature curve, with the temperature fluctuating between 97.6° F. and 99.4° F., rarely above 100° F. Within this comparatively small range the differential blood-count gives a picture which is somewhat difficult to interpret. Lymphocytosis is the feature common to the great majority of the cases, with a temperature below 99° F. When the temperature exceeds 99° F. (and is still below 100° F.) there may be a pronounced polymorphonuclear leucocytosis—more frequently the count is but little altered. But should the temperature become outspoken, and reach 101° F. or 102° F.—a very rare occurrence in this type—then the fluctuation in the quality of the white cells varies as it does in the pyrexial stage of class A (1), and some doubt may at once be expressed as to whether the case does not really belong categorically to the A (1) class. The actual percentage of lymphocytes may be anything from 35 per cent. to 50 per cent.; the highest percentage in my series was 54.4, with a temperature at 98.2 F.

The existence of a sustained lymphocytosis in the presence of a temperature fluctuating between 98° and 100° F., with symptoms of pains in the head, back, and legs, especially in the shins, may be taken as typical of the irregularly relapsing form of trench fever.

As the cases were seen from day to day in the wards, and differential blood-counts made in so many instances, it became evident that from the general group of cases which one was in the habit of labelling the irregularly relapsing type, there emerged a sub-variety which differed from the majority of the cases in two respects. Firstly, the subjective symptoms were much more severe. Shin pains, which are in all forms of the disease severe, became intolerable, and gave rise to much speculation as to whether one was not really dealing with an acute

inflammatory bone disease. One patient told how the pain was so intense that he felt his foot twist involuntarily. It was a common thing to find this same patient rolling on the bed at midnight in agony.

In other cases the weight of the bed-clothes caused so much pain that a cage had to be inserted under the blankets in order to take off the pressure. The loss of sleep consequent upon this suffering led in most cases to a considerable loss of weight and to profound weakness. One had the impression that this class of case might be an aggravated form of Type A (2), more especially as the temperature seldom rose above 99.6° F., and yet the cases were never quite afebrile. Some of these patients gave the history that the pains had always been excruciatingly severe, and certainly no definite evidences of actual initial pyrexia such as is seen in Type B or in Type C could be obtained.

Apparently, therefore, this severe type conforms to the description of shin fever described by some writers, and mentioned also in the report by the Committee, to which reference has already been made.

At the time of admission to hospital it was impossible to say definitely whether the patient was suffering from an aggravated form of irregularly relapsing trench fever, but there was no mistaking the diagnosis from the nature of the subjective symptoms after a few days' observation. These patients formed a class by themselves.

The second respect in which these cases apparently differed from the others was in the differential blood picture. The sum total of the mononuclear cells was frequently equal to, and sometimes in excess of, the total number of polymorphs. The important point, however, was that the transitional and large mononuclear cells were relatively increased. These large mononuclear cells presented nothing abnormal microscopically; they stained clearly, and showed no evidences of fragmentation.

Nineteen per cent. of the cases of irregularly relapsing fever belonged to this group. The highest percentage of large mononuclears (including transitionals) in my series was 28.2 per cent., but 15.2 per cent. was a common figure. Another feature of the differential count in the aggravated form was that, in counts taken during the elevation of temperature, there was a diminution in the percentage of lymphocytes, with a corresponding increase in the percentage of polymorphs. The large mononuclear cells remained approximately at the same level.

I do not propose to discuss at length the significance of this blood picture, but it is a distinct change, and would seem to point to the existence of a separate and probably a specific toxin in these cases, or that we are dealing with a special phase in the evolution of the infecting agent. The observation that the haematological change is confined to a comparatively small percentage of the total number of trench fever cases seen would lend support to the former theory. Pathologically, there is no sound reason why a lymphocyte-producing agent should also stimulate the formation of large mononuclears. Modern haematology claims that the lymphocyte and large mononuclears have a different

genesis, as well as a different function. On the other hand, there are cases in which both lymphocyte and large mononuclears are relatively increased, and if we assume that each class of cell is present in response to a specific infecting agent, then the question of a double infection at once presents itself.

In this connexion it is noteworthy that the regularly relapsing type of fever may be present with the irregularly relapsing form.

*The Total and Differential White Cell Count in Type B,  
i.e. the Influenzal Type.*

This influenza group is not very common at the Base hospitals in France. In my series I have included the cases which gave a history of an initial short bout of fever followed by apyrexia. Most of the cases were still complaining of shin pains when admitted to hospital; all of them gave a history of an abrupt onset with severe pains in the head, back, and legs or arms. That it is not met with more commonly is due, perhaps, not so much to its actual rarity, as to the fact that men recover quickly, and do not require to be evacuated to the rear hospital units.

Obviously this initial type of trench fever may be suggested clinically, and from the chart readings, by the last relapse of a case which has been typically relapsing from the onset, and where the penultimate spasm of fever has not been recorded, as frequently happens during pressure of work at Casualty Clearing Stations. In such cases the previous history is of extreme importance, especially in the time and mode of onset. Of 22 cases of this type, 7 showed a normal differential count with a normal temperature. Clinically these cases were free from all pains and aches, and were in particularly good physical condition.

The remaining cases with a normal temperature gave a lymphocytosis varying from 35 to 63.8 per cent. On four patients coming under this group, I had the opportunity of making differential counts during the period of pyrexia, and the increase in polymorphs and diminution in the number of lymphocytes has been a well-marked feature. In fact, the blood picture would appear to be similar to that met with in Type A (1), the only difference being that the lymphocytosis which follows the fever in Type B remains constantly present, uninterrupted by polymorphonuclear excess, until the patient has presumably combated his infection, when the counts return to normal limits. The total count in this series varied between 7,200 and 20,937 cells per c.mm.

It has been observed from the temperature charts that cases belonging originally to Type B have occasionally taken on the characteristics of Type A (2), i.e. the irregularly relapsing type, but uncomplicated cases of Type B undoubtedly do occur, and represent trench fever in its mildest form.

*The Total and Differential White Cell Count in Type C, i. e. the so-called Enteric Type.*

This type has certain features in common with the paratyphoid group of infections. The illness begins, often indefinitely, with a long remittent fever. The patient lies in bed in a listless condition, apparently the subject of a moderate toxæmia. There are no outstanding objective signs from the physical examination, but tenderness over the left hypochondrium is more common in this group than in any of the others, and diarrhoea has been present in a few cases. I have notes of 13 cases of this type, and am consequently loath to draw any conclusion from so small a number. All of these patients complained of different aches and pains, involving the head, back, and limbs, especially the shins.

Agglutinations did not reveal the presence of a paratyphoid infection in four cases examined. The pulse-rate varied from 90 to 100 per min., and was not dicrotic. In other respects also the illness seems to differ from the enteric group. Diet, for instance, has no appreciable influence on the course of the fever, and no acute abdominal symptoms have ever been recorded, even when patients have been having a full diet very early in the disease. The total white cell count varied from 7,000 to 25,000 cells per c.mm.; 14,000 was a common figure. From the records of 18 differential white cell counts, it may be said that lymphocytosis (absolute and relative) has been the common finding. During the intermittent fever which is seen in the first week of the illness, the polymorphs are increased, and definitely so, even with a temperature of 99.4° F. The liability for this type of case to develop an accelerated action of the heart is noted below.

The leucocytosis, with polymorph excess during fever and lymphocytosis in the apyrexia stage, would appear to be a useful factor in helping to eliminate paratyphoid fever—a point of some importance in view of the increasing difficulties attending the technique of agglutinations.

The following case, taken from my series, shows the difficulties which one may meet in this group:

Pte. T. came into hospital on 15.3.18 complaining of pains in the head and back of five days' duration. It was somewhat difficult to get an accurate statement of the onset of the illness, for the patient was very drowsy and apathetic. It was learned, however, that a short time prior to his evacuation from the line, he was verminous and had his clothes treated with cresol. His general condition was poor. The skin surface was hot and flushed, and small petechiae were found over the trunk and legs. No rose spots were detected. The tongue was furred, but there was neither sickness nor vomiting. The abdominal reflexes were feebly marked, and deep palpation in the right iliac fossa elicited slight tenderness. He had no diarrhoea, rather constipation, and the spleen was not enlarged. On the second day after his admission to hospital, a few rhonchi were heard at the bases of both lungs, but there was nothing else



abnormal in the chest. The pulse was not dicrotic or irregular. Agglutinations, made on 23.3.18 and again on 28.3.18, negatived paratyphoid fever. On 1.4.18 he was much better, and was able to state that he had had severe pains in back and legs since 8.3.18 so far as he could remember. These pains never left him whilst he was in hospital; they became localized to the legs, and more particularly to the shins.

*Blood Examination:*

Date.	Total.	Polys.	Eosinos.	Lymphs.	Large Monos.	Temp.
17.4.18	14,375	43.4	1.3	48.6	6.3	98.6° F.
18.4.18	14,800	50.3	1.0	44.0	4.6	98.6° F.
20.4.18	15,200	48.3	1.6	43.3	6.6	97.0° F.

*The Incidence of D. A. H. as a True Sequel of Trench Fever, and the Blood Condition in such Cases.*

There is a gradually accumulating mass of evidence to prove that an accelerated action of the heart is one of the occasional accompaniments and sequelae of trench fever. Apart from the slight disturbances in rate which are common in the early stages of convalescence from all febrile illnesses, we have to deal with a condition here which is in some cases temporary, but in others, unfortunately, of a more permanent nature. It would seem, further, that many cases of D. A. H. invalided to Base hospitals in France as 'D. A. H. following influenza', or 'D. A. H. following rheumatism', are in reality old or recent trench fever infections manifesting themselves in a more subtle form. In the vast majority of cases there is definite complaint made of leg or lumbar pains during the course of the D. A. H., and practically each gives the history of limb pains at a date prior to the onset of the D. A. H. I do not deny that a tachycardia of the most severe type may not be found consequent upon influenza or rheumatism, but I feel convinced that the percentage of cases which one sees in France arising secondarily to these causes is extremely small.

I have noted 54 cases of D. A. H. which have at some time or other been associated with trench fever in one or other of its manifestations. An attempt has been made to trace, as far as possible, the type of trench fever which has preceded or accompanied the D. A. H., and blood-counts, total and differential, have been made in every case.

Altogether 71 total and 85 differential counts have been made.

The table printed on p. 328 gives the relative percentages of D. A. H. cases found in the various types of trench fever. For comparison I have also introduced the results quoted by the special Committee on trench fever.



*The Percentage of D. A. H. Cases associated with the Various Types of Trench Fever.*

	Type A (1). The Regularly Re- lapsing Form.	Type A (2). The Irregularly Re- lapsing Form.	Type B. The Influenzal Form.	Type C. The Enteric Form.	Doubt- ful. ? Form.
The Committee's series	26.3 %		48.1 %	30.7 %	
The present series	17.8 %	29.3 %	22.7 %	23 %	4 cases

The total white cell-count has the characteristics associated with that found in Type A (2), that is, it is variable, but on the whole it tends to be high. Here again there is a tendency for each particular case to have its own limitations in leucocytosis. As is to be expected, very few counts, total or differential, were made during the period of fever, for pyrexia is not very often found when the disordered action of the heart sets in permanently. If a rise of temperature does take place, it is rarely pronounced, and the fluctuation in the total white cell count is not marked, unless the case belongs to the regularly relapsing form, in which case the blood picture undergoes the changes described as typical of the pyrexia stage of that form of the disease. Concerning the differential count it may be said that lymphocytosis is the rule, so long as the temperature remains normal. The highest percentages of lymphocytes are found in cases of D. A. H. Occasionally one meets with a large mononuclear excess in cases of D. A. H. Two cases in my series showed this phenomenon. As a general rule there is not much pain in the head, back, or legs associated with the tachycardia, but this is not always so. I have notes of one patient who had pains in the legs so severely that I had no hesitation in classifying him in the aggravated form of Type A (2). The temperature chart was typical of the irregularly relapsing form of the fever described above. The large mononuclear cells reached 15.6 per cent. in this case, but as time went on, and with rest in bed, the large mononuclears dropped to 6 per cent., although the lymphocytes remained approximately at the same percentage. Simultaneously the pains became less severe, and on discharge the only symptoms were accelerated pulse-rate, poor response to effort, slight shin pains, and lymphocytosis. From an analysis of the charts and blood-counts at my disposal, I find no evidence to prove that the extent of lymphocytosis is always proportionate to the degree of acceleration of the pulse-rate, and consequently one cannot suggest that the differential blood-count can be reckoned upon as a guide to the amount of intoxication. I have found, however, that it is a mistake to allow patients with a pulse-rate of 90 to 100 per min. at rest in bed to get up when the lymphocytes are relatively and absolutely increased. These are the cases most likely in my opinion to develop D. A. H. If exercise is to be taken at all, it must be of the most carefully-graduated type, and only when there are evidences of slight intoxication; and until a better method is brought to our notice, I suggest that the differential blood-count may be of some assistance at least in helping us

to say whether, in the presence of a normal temperature and pulse-rate, the patient is really free from infection.

The stage of transition from the normal pulse-rate to that which is typical of 'heart hurry' is a gradual one as a rule. It occurs most frequently during the so-called convalescence, when the temperature is normal. It gives due warning of its appearance, even when the patient is kept in bed, but even absolute rest in bed will not always prevent its continuance once it has started. The majority of the cases, however, only develop tachycardia after being allowed up for a few hours per day, and in these cases a renewal of rest in bed may have little or no effect on the heart-rate. Presumably, at this stage of the disease, the casual agent is in the latent phase, but the toxin produced by it is not harmless, and it does not seem unreasonable to suppose that the mononuclear excess is a clinical sign of some importance in determining its potential powers for producing harm, in the form of a protracted disorder of the heart. The group of D. A. H. cases with symptoms of 'precordial pain, palpitation, accelerated pulse-rate, shortness of breath on exertion, tremor, exhaustion, dizziness, and certain vasomotor phenomena with normal heart boundaries and sounds' is the exact clinical entity seen so frequently in convalescence from trench fever. It was to this syndrome that Sir Clifford Allbutt (1) gave the name of ponopalmosis, and suggested the presence of a toxic agent. The existence of lymphocytosis in these cases is apparently pathological proof of this opinion.

Temporary accelerations in the pulse-rate, such as those described by Major Swift (2), are very common, both during the course of irregularly relapsing type, and after the fever in the relapsing type, and in Type C. These temporary spasms of tachycardia must be considered as evidences of a predisposition on the part of the heart-muscle for involvement in a more permanent instability, and experience has shown that many such cases do actually develop a definite tachycardia.

From an analysis of 54 pulse-charts of D. A. H. cases, temporary tachycardia was found in 34 cases, i. e. in 62.9 per cent. before the condition became a definite entity. It is to be regretted that there are no records in this series to indicate the presence or absence of tachycardia during sleep. Several attempts were made to determine whether there was any alteration in the rate, but the results are not conclusive; it is a difficult manoeuvre.

The recent work of Major Marris (3) has shown the importance of investigating every case of tachycardia. His remarks on this condition as found in cases of typhoid and paratyphoid fevers have given the necessary impetus to further work in the direction of careful analysis of the pulse-rate in various pathological states. Applying what he has said to the classification of cases of D. A. H. following trench fever, it is apparent at once that practically every case falls under the heading of vasomotor tachycardia. The time of onset is late in the disease. The tremor, the perspirations, and even the dermatographia, which are found associated with the tachycardia in certain convalescent cases of paratyphoid, are to be found in the vast majority of cases of D. A. H. subsequent to trench fever infection.

Although some writers have described an enlargement of the cardiac boundaries, and even a bruit at the apex of the heart in D. A. H. cases, I have never found any evidence of such, and do not feel convinced that the accelerated action is ever 'cardiac' in type. It is quite possible that the temporary tachycardia, of which I have spoken above, may be of the so-called postural type, but I have no direct confirmation of this.

In the light of these remarks, it seems apparent that the lymphocytosis found in the cases of D. A. H. under consideration may be regarded as useful signs in determining the existence of a vasomotor toxin rather than one acting directly on the heart-muscle.

*Other Conditions met with in Active Service showing similar Blood Changes.*

The lymphocytosis associated with the typhoid group is well recognized, and has been used frequently for diagnostic purposes, but the leucopenia is also important, and is, in the absence of complications, seldom absent. The recent epidemic of influenza gave me the opportunity of examining the blood of 20 cases at different phases of the disease. In the majority of the patients investigated, the clinical signs were those of diffuse broncho-pneumonia with special involvement of the bases of the lungs—pleurisy, fibrinous and serous, was a common complication. In three cases only were the lymphocytes over 39 per cent., and in one of these there was a concomitant malaria infection. The total count was on an average 12,000 per c.mm. It may be recalled, however, that it is not uncommon to find a relative increase in the lymphocytes after a protracted fever of influenzal origin. No doubt symbiosis of other organisms played an important rôle in determining the polymorphonuclear leucocytosis in this latest epidemic. Malaria paroxysms cause a well-marked polynuclear leucocytosis, very much similar to that found in cases of regularly relapsing trench fever. Certainly the examination of the blood during the elevated temperature would not help to differentiate the two diseases. Total and differential counts taken during the apyrexial stage of malaria are characteristic in that they show a leucopenia affecting both polymorphs and lymphocytes. Towards the end of the apyrexial stage the cells—and more particularly the large mononuclears—are increased relatively. These features of the differential count should suffice to distinguish the disease from cases of trench fever, where large mononuclear excess is the exception rather than the rule.

Captain Miller (4) has shown that in many cases of gas poisoning the degree of lymphocytosis (even up to 60 per cent. with a total count of 17,000) has been substantial. This is an important observation, but one which has not been corroborated so far as I know. In view of the large number of trench fever cases showing a similar blood condition, even in the latent periods of the disease, it would have been advisable to ascertain in every case whether a trench fever infection in any of its various forms could have been eliminated.

The only article in the literature which deals directly with this subject is one by Tate and McLeod (5), who have examined 27 cases of trench fever, and found that during the pyrexial period the polymorphs were increased, and that in the apyrexial stage the blood condition changed to one of lymphocytosis, affecting particularly the small lymphocytes—a change which I have had the opportunity of corroborating, with certain reservations. They state, however, that from examination of 26 controls, 'the usual relative proportions of leucocytes amongst soldiers in France is not the normal of the text-books', and again, 'that errors are likely to be made when differential counts made on soldiers in case of illness are compared with that standard'. With the object of elucidating the question of lymphocytosis more thoroughly, I selected control cases from:

- Group 1. Men admitted to hospital for bacteriological examination of faeces and urine, prior to their being employed as cooks.
- Group 2. Men admitted to hospital with diarrhoea.
- Group 3. Men in the unit to which I am attached.
- Group 4. Men suffering from other diseases, i.e. chronic arthritis, bronchitis, gastric ulcer, &c.

Careful notes were taken in every case, and special attention was given to the possibility of the man having had trench fever, or D. A. H. as a consequence of trench fever, at any previous time. The results of the work on this control series have been most interesting, and have incidentally opened up another branch of research. The men of the first and second group were examined in the wards in the usual fashion, and specimens of the stools were sent on three consecutive days for bacteriological examination by Major Anthonisz, Assistant Advisor in Pathology to Calais Area. It would be impossible to go into the detailed results of the findings in this paper; space would not permit of my doing so. Suffice it to say that in 119 cases in Group 1 there was a normal differential blood-count in 33 cases only. In the remaining 86 cases, the lymphocytosis, which was nearly always relative only, could be explained by previous trench fever or D. A. H. or 'chronic rheumatism since coming to France' in 42 cases. Differential and total white cell counts were done in 17 cases in Group 2, i.e. men admitted to hospital with symptoms of diarrhoea. Seven cases gave a normal differential white count with a normal temperature; in the 10 remaining cases relative lymphocytosis was the common feature. Of the 54 cases showing lymphocytosis in Groups 1 and 2 no satisfactory explanation could be reached in 11 cases. Major Anthonisz has examined the stools in all of these and has found a considerable divergence from normal in 43 instances. It is too premature, however, to indicate the findings in this part of the work which is as yet incomplete. It was thought from the result of these observations that it would be advisable to examine the blood and stools in men who could be observed from day to day, and who could be examined at leisure. The men chosen for this purpose were derived from the unit. The practical difficulties are enormous. Blood-counts, total and differential, have been made in 62 cases. In 22 of these there was no

deviation from normal in any particular; in 7 cases there was a definite history of trench fever, or D. A. H. following trench fever, and an accompanying lymphocytosis. The 33 men remaining all show lymphocytosis to some extent; they are being investigated at present by Major Anthonisz from the bacteriological standpoint.

Group 4 controls were taken from the wards of the medical and surgical divisions. The patients—20 in all—were admitted to hospital with conditions such as cellulitis of the hand, chronic arthritis, bronchitis, and gastric ulcer, &c. After eliminating trench fever from the history, all but one showed a normal total and differential count. This particular case in question gave 39 per cent. lymphocytes. The stools, however, were not examined in this case.

#### *Summary.*

1. The conclusions arrived at in this paper have been made after a continued clinical and haematological examination of 438 soldiers, including controls; altogether 515 total white cell counts and 607 differential counts were done.

2. Lymphocytosis during the apyrexial periods and polymorphonuclear leucocytosis during the pyrexial periods is the condition found in the regularly relapsing type of trench fever (Type A (1)).

3. Cases of regularly relapsing trench fever and of the influenzal type (Type B) may merge gradually into the irregularly relapsing form (Type A (2)).

4. In the irregularly relapsing type there is no such definite fluctuation in the cells as is found in the regularly relapsing type. The existence of sustained lymphocytosis in the presence of a temperature swinging between 98 F. and 100 F., with symptoms of pain in the head, back, and legs, especially in the shins, may be taken as typical of this form of trench fever.

5. A normal differential blood-count in the absence of fever and subjective symptoms may be regarded as proof of the absence of trench fever infections.

6. A certain proportion of cases of irregularly relapsing trench fever show an excess of large mononuclear cells. These cases are accompanied by very intense shin pains.

7. The influenzal type of trench fever is the mildest form of the disease.

8. The total white cell count in Type C (the enteric type) is moderately high. In addition, polymorphonuclear leucocytosis is present during the fever. These points serve as useful guides in the differential diagnosis from enteric infections.

9. The vast majority of cases of D. A. H. following trench fever show lymphocytosis, but this is present before onset of D. A. H.

10. Temporary accelerations of the pulse-rate when the patient is at rest in bed, and especially when he is afebrile, are evidences of a predisposition on the part of the heart for involvement in a more permanent instability.

11. Trench fever can be separated from malaria and influenza by repeated blood examinations.

For permission to publish these notes I am indebted to Colonel Wilson Ranson, D.S.O., A.M.S.; and to Colonel Cummins, Advisor in Pathology, I am grateful for many valuable suggestions. The assistance given in the laboratory and in the wards by Corporal E. S. J. Glass, R.A.M.C., has been at all times invaluable, and for much of the clerical work entailed in the research I am grateful to Staff-Sergeant Bunce, R.A.M.C.

#### REFERENCES.

1. Allbutt, Clifford, *Brit. Med. Journ.*, July, 1917, ii. 139.
2. Swift, Major, *Res. Soc. of Amer. Red Cross*, 1917.
3. Marris, Major, *Lancet*, Lond., 1918, i. 667.
4. Miller, Capt., *ibid.*, Lond., 1917, i. 793.
5. Tate, D. L., and McLeod, J. W., *ibid.*, 1918, i. 603.



## THE RESPIRATORY METABOLISM IN A CASE OF PROLONGED UNDER-NUTRITION

By J. JOFFE, E. P. POULTON, AND J. H. RYFFEL

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### *Introduction.*

DURING the past three years nearly all diabetic patients at Guy's Hospital have been systematically treated by fasting and subsequently adding increasing quantities of food to their diet until they ceased to lose weight, a method that has gained general acceptance owing to Allen's work.

An unexpected result has been that patients have been able to lead fairly active lives on diets the calorie values of which, when calculated from Atwater's table, show remarkably low values.

In one case mentioned in this year's Goulstonian Lectures (1), a young man aged 27 had put on 9 lb. in weight since his fasting treatment one year previously. His weight was constant on a diet of at most 2,000 calories a day, and one day each week it was lower than this. The heat value of the food concerned was 34 per kilo. He lived an out-of-door life. He walked about five miles a day at the rate of one mile in seventeen minutes. Twice a week he rode for ten miles. In general he took about the same amount of exercise as the average person not employed in manual labour, does in the country.

The problem that presented itself was whether, in individuals who had for a long time lived on low calorie value diets, the ordinary occupations of life were carried out more efficiently than usual, i.e. with a less expenditure of energy.

If this were the case, there would be two possibilities: (1) the resting metabolism in the post-absorptive state (i.e. twelve hours after the last meal) might be unusually low; (2) the output of heat corresponding to a given amount of muscular work might be diminished, i.e. muscular work might be carried out with greater efficiency than normal.

It is well known that the output of heat calculated per kilo of body-weight is variable, but that more constant values are obtained if the output per unit of surface area is used.

<sup>1</sup> The expenses of this investigation were defrayed by a Government grant to one of us, E. P. P., from the Royal Society.

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The following table is compiled from the results of metabolism experiments on healthy men collected by Magnus Levy (2) from the literature :

TABLE I.

Body-weight.	Calorie output per kilo for 24 hours.	No. of individuals observed.
Kilos.	(average)	
43-53	27.7	4
53-63	25.5	7
63-73	23.2	13
73-83	22.9	4
83-90.4	20.8	3

Variations of 10 per cent. from the average heat values are met with under physiological conditions.

Benedict (3) has shown that in complete starvation there is some diminution in the heat output at rest.

## Subject L.

Average of 4 days' normal diet immediately before the fast :

Body-weight.	CO <sub>2</sub> .	O <sub>2</sub> .	Respiratory	Cals.	Cals. per kilo
Kilos.	c.c. per min.	c.c. per min.	Quotient	per 24 hours.	per 24 hours.
60.5	191	300	0.85	1554	25.7

Average of last 6 days of 31-days' fast :

48.2	123	158	0.73	1131	23.5
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The metabolism of L corresponding to his body-weight was normal before the beginning of the fast, but was rather under normal, though not very much under, at the end, viz. 23.5 instead of 27.7, which is the figure corresponding to his body-weight in Magnus Levy's table.

It was thought to be quite possible that considerably lower results would be obtained in states of under-nutrition carried on over considerable periods.

Magnus Levy (4) examined a man, aged 19, who had latent phthisis, and had eaten very little for nine months for fear of constipation. The patient weighed 36 kilos and the calorie output per kilo was 23.1. This rose to 28.7, a normal figure when the patient's weight had risen to 52.2 (Table II).

All through this paper the heat output is calculated in calories from the respiratory exchange according to Zuntz and Schumburg's method (5), making no allowance for the protein metabolism, which was very low in the case investigated in this paper. Recently Dubois's 'Height-weight' formula (6) for the body surface has often been used; it is claimed that this is more accurate than Meeh's formula. Using Dubois's formula for calculating the calorie output per sq. m. body surface per hour in Magnus Levy's case, the value was 26.6 during the first period, before the patient had been induced to eat more.

Svenson (7) also obtained low figures for the metabolism of a patient convalescent from typhoid fever, the oxygen intake per minute being 111.1 c.c.

on the second day of convalescence. The values for the fourth and seventh days, which are frequently quoted, viz. 48.3 and 60.8 c.c., are so exceedingly low that it is difficult to imagine that there was not some mistake in the experiments, especially as these figures do not fit in with the rest of the series.

Recently Loewy and Zuntz (8) have shown that the restricted diet in Berlin caused a decrease in their resting metabolism, which had been constant for twenty-five years previously. In the case of Zuntz at rest the calculated calorie output in 1916 on restricted diet was 1,366 per diem, i.e. 22.5 calories per kilo, and in the case of Loewy it was 1,128 cal. or 19.81 cal. per kilo. The fall was greatest in Loewy's case. Before the war his metabolism was rather under the average for his body-weight.

TABLE II. *Resting Metabolism in Cases of Under-nutrition.*

	Wt. Kilos.	O <sub>2</sub> . c.c. per min.	CO <sub>2</sub> . c.c. per min.	R. Q.	Cals. 24 hours.	Cals. per kilo 24 hours.	Cals. per sq. m. (Ht.-wt. formula) per hour.
<i>Magnus Levy's Case.</i>							
Period I. Nov. 16-21. Low diet	36.2	120.6	98.4	0.82	837	23.1	26.6
II. Nov. 23-Dec. 9. Liberal diet	38.0	155.9	127.9	0.82	1083	28.5	33.0
III. Mar. 13-May 8. Normal diet	52.2	215	177.3	0.825	1496	28.7	40.5
<i>Svenson's typhoid convalescent—</i>							
2nd day	35.0	111.1	—	0.639	—	—	—
8th day	35.0	123.9	—	0.792	869	24.8	—
Zuntz, 1910. Normal diet	68.5	234.9	195	0.83	1637	23.9	33.0 *
Zuntz, 1916. Restricted diet	60.6	197.6	154.1	0.78	1366	22.5	29.9 *
Loewy <sup>1</sup> . Normal diet	62.3	—	—	—	1429	22.9	30.3 *
Loewy, 1916. Restricted diet	57	164.8	140.6	0.86	1128	19.8	25.4 *

\* Meeh's formula used.

Loewy and Zuntz argue that the fall in metabolism is not due to diminution in protein metabolism (i.e. the decrease in its specific dynamic action), because in Loewy's case the protein metabolism remained the same. They consider it is due to diminished active cell-substance in the body.

In spite of the work already mentioned it seemed well worth while to examine the matter afresh, especially as in Magnus Levy's and Svenson's cases the subjects were suffering from disease.

We were able to carry out this investigation through the kindness of Sir Alfred Fripp, who introduced to us a gentleman, Mr. A., aged 47, an enthusiastic vegetarian who had for some years lived mainly on a diet of uncooked fruit, vegetables, and nuts. He was a thin man, 9½ stone in weight (60 kilos), 5 foot 8 inches (171.8 c.m.) in height. He had a considerable scoliosis and kyphosis.

<sup>1</sup> Previous to 1914.

Caspari (9) carried out an elaborate series of investigations on a vegetarian, a man aged 50, who was rigidly isolated during two and a half months. During the first two periods, which lasted for sixty-two days, the subject took rather less than 1 kilo of grapes or apples each day. The nitrogen content of the diet was about 1.2 gm., and the calorie value 780 or 650. There was a daily loss of 3 gm. nitrogen, and the body-weight fell steadily from 53.6 to 41.2 kilos. During the third period, which lasted for fourteen days, apples, figs, and oranges were eaten, the food nitrogen being about 4 gm. and the calorie value about 1,600. He was found to be in nitrogen equilibrium, and had ceased to lose weight. No accurate figures for the respiratory exchange could be obtained, but the calorie value and protein content of the food, urine, and faeces were determined, so that a complete balance could be made out.

It was impossible owing to pressure of other work to carry out the present investigation with the same thoroughness, but this was scarcely necessary as the object of the experiment was rather different. It was not desired to find out on how low a diet equilibrium in body-weight and protein metabolism could be reached; but rather how much the metabolism diminished, a point that Caspari was unable to investigate directly. During the experiment Mr. A. was accommodated in one of the wards of the hospital. He ordered and prepared his own food himself. He spent his time about the hospital and received his friends; but he often went for short walks outside. On certain days his movements were controlled, one of the nurses being in constant attendance on him. We should like to express our thanks to him for the care with which he carried out his share of the experiment. Table III shows the main features of his stay in hospital for rather more than two months.

For the first twenty-two days of the experiment the calorie value of the diet was usually between 400 and 500 per diem. There was a steady loss of weight. On the twenty-second day (June 7) 1 oz. of pine kernels was added to the daily diet, and on the twenty-ninth day (June 14) 2 oz. of pine kernels were added, and this was continued to the end of the experiment. The calorie value of the diet approximated to 1,000. The weight became constant on June 15 (one month from the start) at 120.6 lb., just 12 lb. less than his original weight. His weight remained constant for the next six weeks.

All the food taken was uncooked. The vegetables were cut up to form a salad, and the fruit was either made into a similar salad or eaten whole. The pine kernels were either added to the salads, or ground up to form a cream and taken with the fruit salad.

The vegetables and fruit taken were greens, carrots, beets, onions, radishes, marrow-fat peas, tomatoes and cucumber, apples, oranges, bananas, strawberries, raspberries, currants, and cherries.

The following is a sample of the daily diet:—pine kernels 60 gm., strawberries 180 gm., oranges 320 gm., cherries 60 gm., bananas 160 gm., vegetable salad 215 gm.

Nearly every day the urea in the urine was estimated by the hypobromite

TABLE III.

Day.	Weight. lb.	Average Loss of Wt. lb.	Diet.		Urine.			Volume. c.c.	Diacetic Acid.
			Calories.	Protein N. gram.	N. h. gram. per diem.	Average N. h. gram. per diem.	Average N. K. gram. per diem.		
1	132.62	—	—	—	—	—	—	—	—
2	132.00	0.65			5.06	4.97	5.015	350	+
3	130.81				5.88			550	+
4	130.19				3.98			540	+
5	130.06*	0.93	400	1.02	2.67			375	less
6	128.44				5.08			860	"
7	128.19				4.86			750	"
8	128.19	0.16	346	0.81	5.72		4.06	500	"
9	126.81*				—			800	"
10	126.81				3.47			560	slight
11	126.31	0.545	474	0.93	3.87	3.09	3.20	493	"
12	127.37				3.87			493	"
13	125.81*				3.96			710	"
14	125.81	0.54	474	0.93	2.40	2.96	2.92	650	trace
15	125.69				3.28			700	"
16	125.19				2.74			720	"
17	123.94*	0.62	400	0.95	3.38	2.96	2.92	850	slight
18	124.19				2.55			700	"
19	123.56				2.55			700	"
20	122.94	0.18	410	0.90	3.35	3.10	3.09	980	"
21	123.44				3.04			530	trace
22	123.06*				4.00			670	nil
23	122.56	0.41	710	1.63	3.62	3.10	3.09	860	"
24	123.56				3.99			960	"
25	121.56*				1.84			540	"
26	122.06	+0.06 ‡	577	1.44	2.11	4.14	4.01	860	"
27	121.94				2.52			1080	"
28	121.12*				2.18			1110	"
29	119.62*	0.41	602	1.31	2.21	3.6	3.6	730	"
30	120.62				—			620	"
31	120.00				6.65			1060	"
32	120.12	+0.06 ‡	774	1.82	4.10	4.14	4.01	560	"
33	120.50*				3.89			920	"
34†	—				4.41			1020	"
35†	—	+0.06 ‡	870	2.26	—	4.14	4.01	—	"
36	119.25*				—			—	"
37	120.50				4.18			1080	"
38	120.39	0.62	790	1.79	3.19	3.10	3.09	860	"
39	120.31				—			725	"
40	121.06				2.06			725	"
41	120.69	0.62	890	1.79	4.38	2.34	2.34	1220	"
42	—				3.93			980	"
43	120.44				6.23			1445	"
44†	—	0.62	880	2.00	—	2.34	2.34	—	"
45†	—				—			—	"
46	122.94*				2.42			1580	"
47	123.56*	0.62	960	2.42	7.29	2.34	2.34	1135	"
48	121.69				4.71			660	"
49	121.44				3.94			1145	"
50	121.81	0.62	1080	2.56	7.74	2.22	3.19	610	"
51	121.44				2.22			550	"
52	121.56*				3.38			—	"
53†	—	0.62	1150	2.77	—	2.34	2.34	—	"
54	122.31*				2.08			570	"
55	121.31*				1.88			910	"
56	121.75	0.62	940	2.03	2.96	2.34	2.34	590	"
57	121.19*				1.76			—	"
58	121.75				—			660	"
59	121.06*	0.62	967	2.19	1.93	2.34	2.34	—	"
60	121.81				—			—	"
61	122.94				—			—	"
62	122.06	0.62	1020	2.34	2.21	2.34	2.34	1080	"
63†	—				—			—	"
64†	—				—			—	"
65	122.31*	0.62	911	2.02	—	—	—	—	"

\* Bowels opened in the previous 24 hours.

† On these days Mr. A. was away from the hospital.

N. h. = nitrogen determined by hypobromite method with a correction.

N. K. = nitrogen determined by Kjeldahl's method. ‡ There was a gain of 0.06 lb. during this period.

method, and the total nitrogen (N.h.) has been calculated from these urea figures by multiplying by the factor 0.569, and is shown in Table III, column 6. In addition the total nitrogen in the mixed urines of several successive days was determined by Kjeldahl's method. These figures (N.K.) are shown in column 8. As a comparison, the total nitrogen calculated from the hypobromite estimations for corresponding periods have been arranged in column 7. There is very good agreement between the figures in columns 7 and 8, and this agreement justifies the calculation of the total nitrogen for each day from the hypobromite figures in column 6. The protein content and calorie value of the food (columns 4 and 5) were calculated from Atwater's tables. No analyses of the food were made.

It has already been stated that no attempt could be made to control the food taken by Mr. A. with any accuracy. In fact, the figures given in columns 4 and 5 were calculated from data supplied by himself as to the amount of food he was taking. If the results are looked at in the light of an exact metabolic experiment with balance of intake and output, they must be regarded as unsatisfactory for several reasons. In the first place, there was marked irregularity in the nitrogen excretion from day to day, though the nitrogen intake was apparently fairly constant. In Caspari's case the nitrogen elimination from day to day was remarkably constant. In the second place, there was a steady nitrogen loss all through the experiment, even though the weight became constant on and after the twenty-second day. Neumann (10), however, observed the same thing in some carefully conducted experiments on himself. The total nitrogen loss for forty-two days of the experiment was found to be 82.2 grm. This corresponds approximately to  $5\frac{1}{2}$  lb. body tissue. Calculating for the whole period of the experiment (sixty-five days) at the same rate of loss, the total loss of body tissue would be 8.5 lb. Now Mr. A. actually lost 10 lb. in body-weight, but this loss occurred during the first twenty-two days of the experiment, while the nitrogen loss was continuous. This might possibly be explained by the alteration in the fluid content of the body, viz. that in the latter part of the experiment Mr. A. retained enough water to counterbalance his loss of body tissue, but this is not at all a satisfactory explanation. In the third place, it has been pointed out that in the latter part of the experiment the diet had a calorie value of approximately 1,000. Now Mr. A.'s metabolism at rest in bed (see Table IV) was about this figure. Some rough calculations indicating the actual calorie output for twenty-four hours are given in Table V. They were made from notes supplied by Mr. A. as to how his day was spent, i.e. the number of hours he was lying down, sitting, standing, or walking. The mean total energy expended was 1,514 calories in twenty-four hours, i.e. 27.3 cals. per kilo. This figure agrees fairly well with Caspari's figure, viz. 1,435 (average of last six days), i.e. 35.1 cals per kilo, for his vegetarian subject H. H. during Period III, when his weight had become constant and he was in nitrogen equilibrium. Caspari's figures were obtained in quite a different way, viz. from the calorie value of the food actually used by H. H., the heat of combustion of urine and faeces being deducted from the heat of combustion of the food. However, it will be noticed in the case of



Mr. A. that the output of energy for the day was about one and a half times as great as the calorie value of the food taken, and yet Mr. A.'s weight remained constant. This daily loss of 500 calories is equivalent to the combustion of nearly 2 oz. of fat, which would mean at least a loss of 1 lb. in body-weight every eight days.

TABLE IV. *Rest Metabolism of Mr. A.*

Date.	Wt. kilos.	CO <sub>2</sub> . c.c. per min.	O <sub>2</sub> . c.c. per min.	R. Q.	Cals. per min.	Cals. per 24 hours.	Cals. per kilo. per 24 hours.	Cals. per sq. m. per hour.*
May 22	58.3	115.7	153	0.76	0.73	1040	17.9	25.7
June 4, 9.30 a.m.	56	112	160	0.76	0.76	1093	19.6	27.5
5.30 p.m.		122	158	0.77	0.75	1080	19.3	27.2
June 27	54.7	122	154	0.77	0.73	1050	19.2	26.7
July 27	54.8	126	155	0.81	0.75	1070	19.5	27.2
Mean		120	156	0.77	0.74	1066	19.1	26.6

\* Height-weight formula.

TABLE V. *Mr. A.—A day's work.*

	Indirect Calorimetry.			
	CO <sub>2</sub> . c.c. per min.	O <sub>2</sub> . c.c. per min.	R. Q.	Cals. per min.
Lying	122	154	0.77	0.73
Sitting upright, reading and taking notes	152	190	0.80	0.91
Standing relaxed	168	210	0.80	1.00
Standing preparing food	357	397	0.90	1.96
Walking 3 miles per hour	618	763	0.81	3.61

	June 1, 1917.		June 2.		June 3.		July 28.	
	Hours.	Cals.	Hours.	Cals.	Hours.	Cals.	Hours.	Cals.
Lying	9.5	416	12.5	537	10	438	9.58	419
Sitting upright, reading and taking notes	9.25	505	5.75	314	9.17	495	7.74	423
Standing relaxed	0.65	39	0.92	73	0.88	53	1.67	100
Standing preparing food	4.50	527	4.50	529	3.75	441	4.76	558
Walking 3 miles per hour	0.10	22	0.33	71	0.20	43	0.25	54
	24.00	1509	24.00	1524	24.00	1470	24.00	1554

These three discrepancies may be in part explained by the fact that Mr. A. left the hospital on four occasions for one or two days at a time, and there can be no doubt that his diet was relaxed at these times. In fact, on one occasion he actually gained  $2\frac{1}{2}$  lb. in weight in three days. However, it is difficult to see how these absences account for everything, and we can only conclude that some error has crept into the records of the daily food intake. However, of one thing we can be certain, and that is that Mr. A. was subsisting on a diet of very much lower calorie value than the ordinary man is accustomed to, though exactly what the calorie value was is uncertain.

Throughout the experiment Mr. A. stated that he felt quite capable of carrying out severe muscular work, and on one day he ran up and down the four

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flights of stairs in the Pathological Department for  $6\frac{1}{4}$  hours. The work expended in raising the body against gravity was 756,000 foot-pounds. This work was equivalent to climbing up 6,600 feet, which was a considerable achievement. Caspari noticed the same thing with his vegetarian patient H. H. The latter could not take walking exercise, owing to a painful foot which developed shortly after the experiment began. However, he continued gymnastic exercise, and showed remarkable strength.

The explanation probably lies in the fact that vegetarian subjects are naturally enthusiasts, and by an effort of the will are capable of performing feats involving pretty severe muscular work which the ordinary person would feel incapable of performing under the same conditions of diet.

In general, however, it was noticed that Mr. A. preferred to spend his days in hospital quietly sitting, reading and making notes and talking to visitors, with an occasional short stroll in the Park or outside the hospital.

### *The Basal Metabolism.*

The metabolic experiments were carried out in the morning before rising. The patient was awake, but lay absolutely quiet. The Douglas bag method was used, the expired air being measured by a previously standardized gas meter. Haldane's smaller gas analysis apparatus was used for the analyses of the samples of expired air.

On each occasion four or five determinations were carried out. It was found that this number was usually necessary before constant results were obtained. On June 4 Mr. A. remained the whole day in bed. There was no perceptible difference between the morning determinations and those in the late afternoon an hour or two after his meal. Hence there was no marked periodicity at different times of the day. The results are shown in Table IV.

Throughout the whole series of experiments, which ranged over sixty-five days, the resting metabolism in the post-absorptive state calculated per kilo of body-weight was constant, the mean being 19.1. This is quite a low figure, since the mean for this weight is 25.5 per kilo. Unfortunately there are no figures for the resting metabolism of Mr. A. on a normal diet for comparison. This figure 19.1 is strictly comparable to Loewy's reduced metabolism—a man of about the same weight as Mr. A. When the metabolism is calculated per sq. metre of body surface by the height-weight formula, the figure for Mr. A. is very similar to Loewy's and to Magnus Levy's cases, viz. 26.6.

One noteworthy fact about Mr. A. was that his minimum metabolism was reached seven days after his special diet was begun, when he had only lost 2 kilos in body-weight. This suggests that owing to his habitual low diet his metabolism was always at a low level.

An attempt to find out whether the low protein metabolism was responsible for these low figures, owing to the absence of its specific dynamic action, was unsuccessful, as the administration of a large dose of plasmon made Mr. A. feel very ill, and the experiment could not be continued.

It was noticed that the pulse was always below 50 when the patient was resting in bed. This is a point that has been emphasized by Benedict in starvation.

*The effect of prolonged under-nutrition on the efficiency of muscular work.*

Lusk (11) has shown that in dogs after a period of starvation the efficiency of muscular work is unaltered, though the basal metabolism is diminished. We have been unable to find any observations on this point in man. It was possible, in cases of prolonged under-nutrition, some adaptation might take place in the direction of increased efficiency. Mr. A. was a suitable subject for this investigation owing to his long-established dietetic habits. The Douglas bag method was again used. J. H. R., weight 8 stone 13 lb. (56.8 kilos) and height 5 feet 8 inches (172.7 cm.), of similar build to Mr. A., acted as a control. A roughly oval course of 220 feet was marked out in the Park, and the subject of the experiment walked at three, four, or five miles an hour, carrying the Douglas apparatus on the back. In the first experiment a straight track was chosen and the subject walked backwards and forwards along it. The rate of walking could be most accurately controlled by an observer with a stop watch, who walked round at the same time and set the pace.

To obtain the heat output at the different rates of walking the value for the subject standing at rest in a relaxed position was subtracted from the values obtained while walking. Dividing this by the body-weight (including the weight of the clothes and apparatus) and by the rate of walking in metres per minute, the result is expressed in calories per kilogrammetre of horizontal movement. These values are plotted against the rate of walking. (See diagram and Tables VI and VII.)

Douglas (12) made two experiments on himself at Oxford at different seasons of the year with very different results. They are shown by the continuous lines in the diagram; the efficiency is obviously greater in the lower line, where the experiments were carried out round a circular track in the laboratory, than in the upper line, where a grass track backwards and forwards was used.

Benedict's subject B II (13) agrees very well with Douglas's lower curve. The results for his subject B I (four experiments shown in diagram at rather under 3 miles an hour) lie between the two curves. All the experiments were carried out on a moving platform.

In the case of Mr. A. and J. H. R. the results at 3 and 5 miles an hour agree very well with Douglas's lower curve and with Benedict's figures. Most of our experiments were carried out at 4 miles per hour, and these show remarkable variations on different occasions, although here again there is no difference between the subject of the experiment, Mr. A., and J. H. R., the control, who was living on a normal diet. It will be noticed that when the subject was standing relaxed the heat output was much less in the case of Mr. A. than in the case of J. H. R. The mean of all experiments with Mr. A. was 1.018 cal. per min.,

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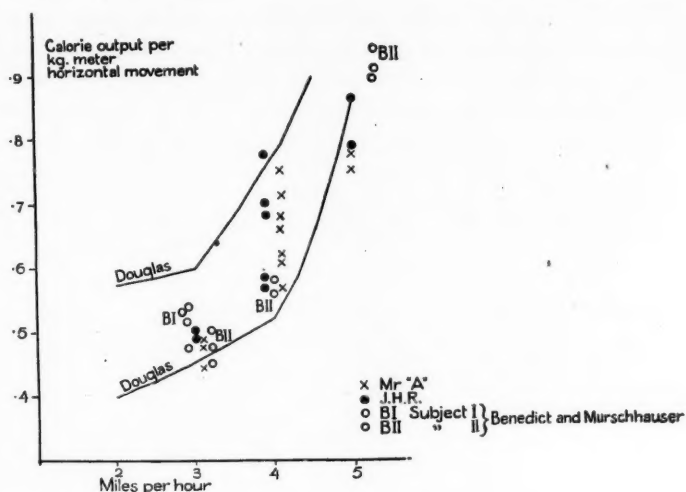


TABLE VI. *Exercise Experiments. Mr. A.*

Date. Weight trans- ported (kilos).	Remarks.	CO <sub>2</sub> . c.c. per min.	O <sub>2</sub> . c.c. per min.	R. Q. cor- rected.	Cals. per min.	Gramme cals. per kilogram- metre.
1917						
May 23	Standing relaxed	180.7	237.3	0.762	1.129	
65.5		170.9	220.9	0.772	1.053	
	3 miles per hour back- wards and forwards	590.6	708.7	0.832	3.43	0.444
		650	799	0.814	3.676	0.491
	Standing relaxed	132.4	165.9	0.798	0.796	
		128.8	166.5	0.774	0.794	
	4 miles per hour back- wards and forwards	995.9	1276	0.781	6.097	0.755
		980.2	1145	0.788	5.479	0.666
May 29	Standing relaxed	223.1	251.7	0.886	1.235	
64.5		204.2	243.6	0.836	1.18	
	3 miles per hour on circular track	614.7	780	0.788	3.733	0.487
May 30	Standing relaxed	145.7	191.1	0.762	0.909	
64.4		160.3	200.2	0.801	0.961	
	4 miles per hour on circular track	963.5	1169	0.824	5.647	0.682
		1049	1209	0.867	5.901	0.719
	Standing relaxed	171.1	210.9	0.811	1.015	
		173.9	196.2	0.886	0.963	
	5 miles per hour on circular track	1306	1544	0.846	7.495	0.753
		1279	1602	0.799	7.687	0.776
July 2	Standing relaxed	174.5	205.4	0.851	0.999	
64.0		197.3	215.9	0.914	1.067	
		188.5	215.8	0.874	1.055	
	4 miles per hour on circular track	902	1075	0.839	5.211	0.614
		880.7	1097	0.803	5.270	0.623
July 23	Standing relaxed	200.6	222.4	0.902	1.096	
64.0	4 miles per hour on circular track	853.2	923	0.924	4.572	0.506
	Light clothes	903.5	1071	0.844	5.197	0.573
66.74	Heavy clothes	1189	1430	0.832	6.922	0.813

while in the case of J. H. R. it was 1.261. This diminution in the case of Mr. A. must be due to the same factors as produced a low basal metabolism. The conclusion is that prolonged under-nutrition causes no alteration in the efficiency with which muscular work is carried out.

TABLE VII. *Exercise Experiments. J. H. R.*

Date. Weight trans- ported (kilos).	Remarks.	CO <sub>2</sub> . c.c. per min.	O <sub>2</sub> . c.c. per min.	R. Q. cor- rected.	Cals. per min.	Gramme cals. per kilogram- metre.
1917						
May 23	Standing relaxed	245.5	298.2	0.843	1.447	
65.5		226.3	262.5	0.862	1.28	
	4 miles per hour back- wards and forwards	1168	1284	0.910	6.338	0.709
		1132	1233	0.919	6.10	0.677
June 6	Standing relaxed					
65.5	12.15 p.m.	176.2	220.3	0.80	1.06	
	4.45 p.m.	201	247.1	0.813	1.19	
		233.5	285.9	0.817	1.38	
	3 miles per hour on circular track	674.6	773	0.873	3.78	0.487
	Standing relaxed	716.2	788.8	0.908	3.89	0.499
	6.18 p.m.	211.7	249.4	0.849	1.21	
	4 miles per hour on circular track	956	1097	0.871	5.36	0.583
		912	1080	0.845	5.24	0.572
	5 miles per hour on circular track	1642	1779	0.923	8.81	0.860
		1401	1669	0.844	8.10	0.787
1918						
Sept. 25	4 miles per hour on circular track					
63.75	<i>Light clothes</i>	1168	1153	1.014	5.82	0.667
		1037	1092	0.949	5.44	0.611
69.43	<i>Heavy clothes</i>	1211	1237	0.979	6.213	0.665
		1257	1262	0.996	6.36	0.685
Oct. 7	<i>Light clothes</i>	1189	1214	0.980	6.094	0.732
61.5		1186	1241	0.956	6.194	0.743
Oct. 8	<i>Heavy clothes</i>	1373	1449	0.952	7.23	0.812
63.5		1302	1346	0.967	6.74	0.746

It was thought that the wide variations in both Mr. A. and J. H. R. at 4 miles an hour might be due to varying climate conditions. Examination of the records from the Meteorological Office did not show sufficient change in temperature, wind, &c. to account for these variations.

However, it was decided to investigate the matter experimentally (see Tables VI, VII, and VIII). In the first case Mr. A. walked at 4 miles an hour wearing as few clothes as possible, viz. shirt and trousers. The rectal and skin temperatures were taken before and after. The rectal temperature remained unaltered, the temperature of the skin of the body and hand had fallen, but the temperature of the face had risen. The calorie output per kilogrammetre, viz. 0.506, was the lowest recorded at this rate of walking. Immediately afterwards very thick clothes were worn. After the exercise the rectal temperature had risen by 0.15° F., and there was a rise in the skin temperature of the body and hand, but a slight fall on the face. The calorie output was rather higher in the first experiment under these conditions, viz. 0.575. However, in the second experi-

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nent a very high value of 0.813 was obtained, which was the highest value found in the case of Mr. A. at 4 miles per hour. It is of course possible that an additional factor entered into this last experiment, viz. fatigue, considering the amount of clothing Mr. A. was wearing. Zuntz and Schumburg (5) have shown the effect of this factor in diminishing the efficiency of muscular work.

TABLE VIII. *The Effect of Clothes and Muscular Exercise on Body Temperature.*

Temperature Observations.								
Subject and Date.	Nature of Clothes.	Rectum. °F.	Left Side of Chest. °C.	Right Side of Chest. °C.	Left Side of Abdomen °C.	Right Hand °C.	Right Side of Face °C.	Remarks.
Mr. A. 1917 July 23	Shirt, trousers	99.8	36.5	35.3		35.5	32.75	Before exercise After 4 miles per hour
		99.8	35	34.5		32.5	34	
	Thin vest, 2 cambric shirts, 2 pyjama suits, flannel waistcoat and coat, flannel trousers	99.85	37	35.5		34.5	33	Before exercise After 4 miles per hour
		100	37	36		35.7	32	
J. H. R. 1918 Sept. 25	Vest, shirt, coat, cellular pants, trousers	100	34.75		35.5	29.25	34.75	Before exercise
		100.4	34		34.25	26.5	33.5	After 4 miles per hour, 1st experiment
		100.4	35		33.5	25.5	34	After 4 miles per hour, 2nd experiment
	3 vests, shirt, waistcoat, 2 coats, thick overcoat, 2 pants, trousers	100.4	35.5		35	33.5	35.75	After 4 miles per hour, 2 experiments
Oct. 7	Shirt, waistcoat, trousers	99.4	34.8		35.1	27	35.3	Before exercise
		100	36		35	23	36	After 4 miles per hour, 2 experiments
Oct. 8	2 vests, shirt, waistcoat, 2 coats, light overcoat, 2 pants, trousers	100.4						Before experiment
								J. H. R. walked quickly in laboratory, to get warm
		100.8	37		37	34	35.5	After 4 miles per hour, 2 experiments

As a confirmatory test we have quite lately carried out the same experiment on J. H. R. (Tables VII and VIII). On Sept. 25, 1918 with light clothes the calorie value per kilogrammetre was 0.667 and 0.611. Later on the same day with heavier clothes the values were 0.665 and 0.685, on the whole a slight increase. The rectal temperature was no higher in this latter experiment, but on the whole the skin temperature was slightly raised.

The experiment was repeated on Oct. 7, in light clothes. The values were 0.732 and 0.748. The rectal temperature after the experiment was 100° F., i.e. lower than on Sept. 25; but the skin temperatures were slightly higher, except



on the hand. On Oct. 8 J. H. R. repeated the experiment in heavy clothes. He walked briskly round the physiological laboratory for some minutes before the experiment, in order to get hot. After the experiment, which was carried out on the usual grass track, the rectal temperature had risen to  $100.8^{\circ}$ , and most of the skin was much hotter than on the day before. The calorie values per kilogrammetre were 0.812 and 0.746, which indicated again some increase on the day before. From these observations the conclusion may be drawn that the output of heat per kilogrammetre is slightly increased if sufficient clothes are worn to raise the body and skin temperatures. This factor, associated possibly with the effect of fatigue, may account, at any rate partially, for the variations in the original experiments at four miles per hour.

#### Conclusions.

1. The resting metabolism is considerably diminished in prolonged underfeeding. It may be as low as in complete starvation.

The metabolism, measured in the erect position, in a state of muscular relaxation is also diminished. The pulse is slow.

2. In prolonged underfeeding there is no increased efficiency during muscular work, as measured by the rate of increase in the respiratory exchange at different rates of walking.

3. The heat output during muscular exercise is influenced by the deep and surface temperatures of the body.

#### REFERENCES.

1. Poulton, *Lancet*, Lond., 1918, i. 863.
2. v. Noorden, *Pathologie des Stoffwechsels*, Berlin, 1906, i. 281.
3. Benedict, *A Study of Prolonged Fasting*, Carnegie Publications, No. 203, Washington, 1915.
4. Magnus Levy, *Zeitschr. f. klin. Med.*, Berlin, 1906, lx. 199.
5. Zuntz u. Schumburg, *Physiologie des Marsches*, Berlin, 1901, 361.
6. Dubois, *Archives of Internal Medicine*, Chicago, 1916, xvii. 863.
7. Svenson, *Zeitschr. f. klin. Med.*, Berlin, 1901, xliii. 86.
8. Loewy u. Zuntz, *Berl. Klin. Woch.*, 1916, 825.
9. Caspari, *Archiv f. d. ges. Physiol.*, Bonn, 1905, cix. 473.
10. Neumann, *Archiv f. Hygiene*, München and Berlin, 1902, xlv. 3.
11. Lusk, *Proc. Soc. Exper. Biol. and Med.*, New York, 1916-17, xiv. 92.
12. Douglas, Haldane, Henderson, and Schneider, *Phil. Trans. Roy. Soc., Lond.*, 1913, Ser. B., cciii. 185.
13. Benedict and Murschhauser, *Energy Transformations during Horizontal Walking*, Carnegie Publications, No. 231, Washington, 1915.

#### NOTE.

Since writing this paper, our attention has been drawn to two publications on this subject. Benedict (*Journ. Roy. Army Med. Corps*, 1918, xxxi. 97) observed a low resting metabolism in a group of young men on a diet of low calorie value. No figures are given for the energy output during muscular work. Zuntz and Loewy (*Biochemische Zeitschrift*, 1918, xc. 244) give some recent figures for the energy expended during muscular work in the case of Loewy on a low calorie value diet. They compare these with similar figures for Loewy on a full diet twenty-two years previously, and are surprised to find no difference. They suggest that the reason is that in the older series of experiments the gas-meter weighing 8.9 kilos was carried on the subject's back. However, this very fact makes it difficult to compare the two series of observations at all. In our experiments with Mr. A. and J. H. R. we were particularly careful to see that the conditions of the experiment were the same in the two cases.

# AN INVESTIGATION INTO THE EFFECTS OF WAR NEPHRITIS ON KIDNEY FUNCTION, WITH OBSERVATIONS ON METHODS FOR ESTIMATING THE EFFICIENCY OF THE KIDNEYS

(A Report to the Medical Research Committee)

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- (2) Phenolsulphonephthalein.

THE present paper deals with certain observations on nephritis cases carried out at No. 5 Military Hospital, London. The laboratory conditions here were naturally much better suited for the investigation of this type of disease than was the case in France, and we were enabled to carry out observations on individual patients extending over a period of several months. The chief points on which information was sought were the interpretation of certain tests and the effects of the disease on the kidney function as indicated by the retention of metabolic products.

Our intention was to endeavour to obtain some idea as to the probable prognosis—both immediate and remote—in these patients, and from this point of view the cases were subjected to a thorough examination at frequent intervals.

*I. Methods of Investigation.*

Various tests which will be referred to later were used from time to time, but, since the following methods were found to give the most valuable results in our hands, a short discussion of them at the present stage will render clearer various subsequent statements and save repetition.

In our experience the most useful chemical tests are found to be—

- (1) Estimation of the concentration of urea and non-protein nitrogen in the blood.
- (2) The diastatic content of the urine.
- (3) The concentration of urea in the urine after giving a dose of urea by mouth.
- (4) The chloride content of the urine.

*Blood urea in Nephritis.* One of the most valuable tests we possess for determining the extent of renal inefficiency in a given case of nephritis is the estimation of urea in the patient's blood. In a normal individual, on an average mixed diet, the blood contains from 20 to 40 mg. urea per 100 c.c. of blood. When the renal function begins to fail, a point is reached at which it becomes difficult for the kidney to deal with the urea and other nitrogenous waste products, with the result that the amount of these bodies in the blood tends to increase. With an increased concentration of urea in the blood, the diseased kidney is able to pass as much urea as the normal kidney, so that nitrogenous equilibrium is still maintained.

Thus, it generally happens that, even in a severe case of chronic Bright's disease, the average amount of urea excreted *per diem* is exactly the same as that passed by the normal individual on a similar diet.

The essential difference between the two cases is that in the healthy person the urea is excreted from blood containing the normal amount of urea, while in the nephritic the blood contains excess of urea.

The reason for this need not be discussed here, but it is obvious that if the excretion of urea depends on filtration of the non-colloidal liquid part of the blood through the glomerulus of the kidney, then the greater the concentration of urea per unit of blood, the larger will be the amount of urea passing through into the kidney tubules.

We may also look at this from the point of view of F. C. MacLean (1), who considers that the stimulus required for the excretion of urea in the healthy kidney is furnished by a concentration of 20 to 40 mg. per 100 c.c. blood, but that it requires the stimulus of a higher concentration of blood urea to give the same result in a diseased kidney. Another important factor in the maintenance of nitrogenous equilibrium is the passage of an increased amount of water.

At any rate, it is quite obvious that in many cases the diseased kidney must be able to eliminate the total amount of urea and other nitrogenous products formed in the body, otherwise there would soon be a very much greater concentration of these substances in the organism than is found to be the case.

In short, the chronic nephritic in general eliminates the usual 30 grm. or so of urea per day, just as the healthy individual does, but, while the blood of the latter usually contains less than 40 mg. per 100 c.c., the former may have a concentration of 100 mg. per 100 c.c. or much more.

From this it is evident that no information is to be obtained in an ordinary chronic case of nephritis by estimating the daily amount of urea passed in the urine, for this will depend chiefly on the amount of protein ingested and not on the condition of the kidney. Much information may, however, be derived from an examination of the blood, and it is unfortunate that the teaching at present in vogue to the effect that urea *per se*, even in large amount, produces no deleterious effects on the body, is often accepted as indicating that the amount of urea present in the blood is of no clinical importance. Whether or not urea acts as a toxic substance when present in high concentration is at present unsettled (2), but that the amount of this product present in the blood furnishes us with an excellent index of the efficiency of the kidney is undoubted.

Generally speaking, the other non-protein constituents of the blood (uric acid, kreatinin, purin bodies, &c.) are found to vary roughly with the urea, so that the same information is obtained by estimating the total amount of non-protein nitrogen in the blood. As the estimation of urea is a much simpler and shorter process, it is best adapted for clinical work, and though we have made a considerable number of estimations of non-protein nitrogen in nephritis cases, we have not been able to obtain any clinical information by this method which was not furnished by the simpler plan of estimating the urea alone.

Since we all possess renal tissue largely in excess of the requirements of the body, it follows that the kidneys may suffer considerable damage and yet sufficient renal substance remain to carry on the normal functions of this organ in the usual way. In such a case, no indication of renal inadequacy would be obtained by estimating the blood urea, for the latter would not be increased. When, however, the available tissue is just insufficient to maintain nitrogenous equilibrium with a normal blood urea concentration, the blood urea immediately goes up in proportion to the extent of the kidney lesion.

When the damage to the kidney is insufficient to produce an increase in the blood urea, evidence of inadequate function can be obtained by other tests to be described later.

In recent acute cases of nephritis there is generally some retention of urea if the condition is at all severe, and the blood may show from 50 to 600 mg. per 100 c.c. or even more. In mild cases there is a gradual return to normal, the rate at which this takes place depending on the severity of the condition. In unfavourable cases, on the other hand, the concentration tends to increase, and in such patients the prognosis is often bad in spite of a favourable clinical condition. In a few of our acute cases in which the urea attained a concentration of 250 to 300 mg. apparently complete recovery took place, but in every instance in which the amount exceeded 300 mg. death ensued. In two such fatal cases the first estimation gave a result of about 200 mg. per 100 c.c. blood, but this amount

steadily increased until the blood contained 600 mg. At this point death took place in both. It is worth noting that in neither of these patients did the clinical condition and general appearance give any indication of the gravity of the condition until a few days before death, and, except for the persistent increase of blood urea, a favourable prognosis might have been given.

Though there is a tendency to retention of urea in practically all cases of acute nephritis, this is by no means true of all chronic cases. In this respect there is a very marked difference between the cirrhotic variety of Bright's disease and the true parenchymatous entity. In the latter, as will be fully discussed later, there is little or no tendency for urea to be increased in the blood, while the former often shows this condition to a very marked extent.

*Method of estimating urea in blood.* The estimation of blood urea was carried out by the well-known urease method on the lines described by Van Slyke (3). Instead of using a specially prepared enzyme we made use of finely-ground soya bean meal, which is easily prepared at any time. To 3 c.c. of blood in a suitable test-tube 0.3 gm. of bean meal was added, and the closed tube placed in a water bath at 37°C. for fifteen minutes. Before distilling off the ammonia formed, 4 c.c. of a saturated solution of potassium carbonate, together with 3 gm. of solid anhydrous potassium carbonate, were added to the tube containing the blood. This was found to give a medium of suitable consistency for the passage of the necessary current of air. As an indicator, one drop of a saturated solution of methyl red in 50 per cent. alcohol was employed. In all other respects we followed the directions given by Van Slyke.

The use of soya bean meal simplifies the procedure very materially as the commercial enzyme preparation is not always easy to procure in this country. The meal has the further advantage that it retains its activity unaltered for several months, while the commercial enzyme tends to deteriorate very quickly. The meal yields a small trace of ammonia, which must be allowed for in very exact work. As the result of many experiments it was found that all our samples gave practically identical values under the conditions of the experiment, 0.3 gm. of the ground bean yielding ammonia equivalent to 0.4 c.c. of N/100 acid.

To prevent frothing there is nothing so efficacious as secondary octyl alcohol, and though other preparations have been recommended from time to time they have not yielded entirely satisfactory results in our hands.

*The diastase of urine and the diastatic test.* Though the presence in the urine of a ferment capable of hydrolysing starch was known for a long time it was not until 1908, when Wohlgemuth (4) devised a method for its quantitative estimation, that any attention was paid to the matter from the clinical standpoint. Wohlgemuth, however, recognized that the amount of this substance in the urine was fairly constant, provided the kidneys were acting efficiently, but that diseased kidneys failed to excrete it in normal amount. Since this observation was made, many papers have been written on the subject, the general consensus of opinion being that there is undoubtedly a marked decrease of this ferment in the urine of individuals suffering from nephritis, especially of the chronic interstitial variety.



Like every other test, the diastatic test suffers from certain drawbacks, and cannot of itself be always relied upon to indicate the renal condition. On the other hand, it is, in our opinion, a most valuable aid when used in conjunction with other methods. No doubt, there are healthy subjects in whose urine the diastatic value occasionally varies considerably from the normal, but from an experience of the test extending over six years we have come to the conclusion that some of the difficulties that are supposed to be associated with it are grossly exaggerated. There is little doubt that the average amount of diastase in the urine of the healthy individual is extraordinarily constant within comparatively narrow limits, and it is rare to get values in healthy subjects either below or above the numbers given below. In rare instances where the results are abnormally high some explanation is usually forthcoming if the case is carefully investigated.

*Technique employed.* As the technique of the test is apparently not very well known in this country, details of the method are given here. The following solutions are required:

(1) A 0.1 solution of 'soluble' starch in distilled water. Since different solutions of 'soluble' starch vary in the rapidity with which they are hydrolysed by diastase, it is quite possible that different samples of starch would yield different results with urine. To avoid this error it is necessary to test a new sample of starch with several specimens of average healthy urine. By this means the action of normal urine on any particular specimen of starch can be ascertained. When this is once known there is no further trouble, as the starch does not apparently change on keeping. To avoid the necessity of control experiments it is well to procure a sufficient amount of starch to begin with, and always use the same sample. Generally, specimens of soluble starch manufactured by any of the firms dealing in fine chemicals, will be found satisfactory.<sup>1</sup> The solution should be prepared fresh, as after a few days it deteriorates and is then useless.

(2) A sodium chloride solution of about 1 per cent. strength.

(3) A solution of iodine of about 0.5 per cent. strength.

For the test from 3 to 5 c.c. of urine are required. For an average urine ten test-tubes of equal size are taken, and to each are added decreasing amounts of the urine from 0.6 c.c. to 0.06 c.c. The total volume in each tube is then made up to 1 c.c. by the addition of sodium chloride, and finally 2 c.c. of the starch solution are added to each. The amounts of the different liquids required are as follows. The  $d$  values corresponding to the final readings are given in the last column.

<sup>1</sup> At first we employed Kahlbaum's starch, but since 1914 we have used a specimen prepared by Messrs. Baird and Tatlock which gives almost the same results as the German preparation.



TABLE I.

Number of Tube.	Amount of Urine in c.c. in each Tube.	Sodium Chloride added to each Tube in c.c.	Starch Solution added to each Tube in c.c.	Corresponding <i>d</i> Value.
1	0.6	0.4	2	3.8
2	0.5	0.5	2	4
3	0.4	0.6	2	5
4	0.3	0.7	2	6.6
5	0.2	0.8	2	10
6	0.1	0.9	2	20
7	0.09 = 0.9 c.c. (dil. 1 in 10)	0.1	2	22
8	0.08 = 0.8 c.c. „	0.2	2	25
9	0.07 = 0.7 c.c. „	0.3	2	28
10	0.06 = 0.6 c.c. „	0.4	2	33

For measuring the urine a 1 c.c. pipette divided into hundredths is required. By this means quantities from 0.6 to 0.1 c.c. can be measured directly; for the smaller amounts it is necessary to dilute the urine in the proportion of 1 part urine to 9 parts salt solution and take corresponding amounts of this. For adding the saline solution a small 10 c.c. burette is most convenient, while the starch solution is best added from a 25 c.c. burette.

When all the tubes are ready they are quickly shaken and placed in a water bath at 37° C. for exactly thirty minutes. They are then taken out and nearly filled with cold distilled water to stop the ferment action. One drop of iodine solution is added to each tube, and starting from No. 1, note is taken of the first tube in which a blue tint is observed. This tube contains just that amount of urine which failed to convert all the starch into dextrin under the conditions of the test. The tube next to this, which may be clear or show a reddish tint, is taken as the 'limit', and from this tube the diastatic value is calculated. This so-called *d* value is empirically expressed in units, and represents the number of cubic centimetres of 0.1 per cent. 'soluble' starch solution which the particular urine is capable of digesting in half an hour at 37° C. This value is obtained by dividing the number of cubic centimetres of starch solution used (2 c.c.) by the amount of urine required to digest this amount of starch. For instance, if the necessary quantity of urine was 0.1 c.c., then the diastatic value = 20. For the tubes containing a relatively large amount of urine more than 1 drop of iodine solution will be required, but the necessary amount is soon ascertained by a little practice. At first, it is not always easy to be quite certain which of two adjacent tubes should be taken as representing the limit, but this is of little importance in practice, for what we really want to know is whether the urine is low in diastase, and this is easily ascertained. Very exact readings are unnecessary for clinical work, and it is not essential to put up all the tubes given in the table.

In the healthy the *d* value varies from 6.6 to 30, the average generally being from 10 to 25. It varies to some extent at different times of the day, and on this account it is best whenever possible to test a sample from the total twenty-four hours' urinary output. Corbett (5), who used the test extensively, never found

a higher value than 40 in a healthy individual. Generally speaking, a constant value below 6.6 may be taken to indicate a defective kidney, provided some other condition is not present in the body by which the diastatic content of the blood is lowered. The average  $d$  value of the plasma appears to be between 5 and 10. In a series of fifty-one cases, including normal and nephritic subjects, the following figures were obtained for the plasma :

8 patients =	.	.	.	.	.	5 $d$ value
24    " =	.	.	.	.	.	6   "
18    " =	.	.	.	.	.	10   "
1     " =	.	.	.	.	.	28   "

In the class of nephritis cases in which diastase tends to be retained one expects a value below 6.6 in the urine, and the lower this value is the more serious appears to be the condition of the kidney. We have not yet seen in any subacute cases a high diastatic value associated with a tendency to nitrogenous retention. During the early acute stage of nephritis this test may be normal, as it was in one fatal case. Here, however, the blood value was 28, so that the normal kidney would be expected to give a much higher value than the  $d = 10$  actually found. In some nephritics the diastatic value gradually gets less as convalescence proceeds, and in such cases evidence of progressive degeneration can usually be obtained by other tests. As a rule, it is more or less normal in chronic parenchymatous cases, but is often very low in the interstitial variety of nephritis. In our experience, a patient with a very low diastatic value during the early acute period of the disease does not usually do well, and it is possible that such patients may be suffering from some slight chronic mischief. The results obtained by this test in our cases are given later.

*The concentration of urea in the urine.* From what has been already stated it is clear that no results of value can be expected from estimations of the daily output of urea in chronic nephritis. In the early stages of acute cases there is undoubtedly a marked decrease in the amount of urea passed, but this generally lasts only for a few days, during which time there is a corresponding increase of nitrogenous waste products in the blood and tissues (6). In the subsequent course of certain of these cases a condition is gradually established in which the concentration of urea in the urine is much less than the usually accepted amount. Average urine from a healthy individual on ordinary mixed diet is held to contain roughly about 2 per cent. urea, but it is certain that this figure is too high; in our experience the average for hospital patients with sound kidneys is nearer to 1.6 per cent. than 2 per cent. In nephritics in whom there is a tendency to retain nitrogen, the power of concentration tends to be diminished, a condition well recognized in chronic interstitial disease. This also takes place during convalescence from acute nephritis, and appears to indicate that the kidneys are still suffering from what in some cases must be a progressive form of disease, though ultimate recovery appears to be possible. This loss of power to concentrate urea may not be easily detected in ordinary specimens of urine, but can be readily

brought out by giving the patient from 15 to 20 grm. of urea in a little water and estimating the percentage of urea in the urine passed some time afterwards. This test has been found to give most valuable help in arriving at a conclusion as to the efficiency of the kidneys.

Experiments were first made to determine whether cases with urea retention could be distinguished from those in which the blood urea was within normal limits by differences in the *total amount* of urea passed in a given time after a dose of 10 or 15 grm. The bladder having been emptied, the patient received the dose of urea dissolved in 400 c.c. of water; the bladder was again emptied 4 hours later. In some cases the amount of urea passed in the hour preceding the dose was determined, and from this the 'excess' urea passed in the four hours following the dose calculated. This method failed entirely to differentiate between those patients in whom the blood urea was known to be above the normal and those in whom no such retention had been observed. It was, however, noticed that the *concentration* of urea in the urine after the dose appeared to bear a definite relationship to the severity of the case, patients with urea retention passing a relatively large amount of urine, with a low urea concentration, while patients without retention passed smaller amounts of urine, but concentrated to a considerably higher figure. In patients in whom there had been persistent urea retention, but whose blood at the time of the test showed normal values (presumably cases in which the kidney tissue was considerably damaged), the concentration was lower than was found in patients with little or no earlier retention.

With a view to bringing out this apparent difference of concentrating power and arriving at an estimate of the functional capacity of the kidney as regards urea concentration, the following test was applied to a series of cases. The patient took no food or drink after 7 p.m.; at 6 a.m. he emptied his bladder and received a dose of 15 grm. of urea dissolved in 100 c.c. of water. At 8 a.m. the bladder was again emptied and the concentration of urea in this specimen of urine estimated. The fluids were purposely limited, and the urea dissolved in a small amount of water with a view to producing a maximum urea concentration.

The results of this test in a series of convalescent cases of nephritis are given in the following table. Blood urea concentration and values are included for purposes of comparison. In a series of normal cases the concentration varied from 2 to 3.5 per cent.

TABLE II.

Number.	Nature of Case.	Urea % (2 hours specimen).	Urine (amount in 2 hours) in c.c.	Blood Urea Concentra- tion in mg. per 100 c.c. Blood.	d Value in specimen from 24 hours' Urine.
1	Cases of nephritis in which	2.46	117	34	6.6
2	no retention had been	2.07	121	27	10
3	observed	2.54	80	20	10
4	"	2.93	108	25	5
5	"	2.14	147	30	6.6
6	"	2.38	108	24	6.6
7	"	2.67	127	24	5
8	"	2.07	132	34	5
9	"	2.53	113	31	6.6
10	"	2.50	114	36	2.5
11	"	2.22	126	36	5
12	"	2.16	153	33	6.6
13	Cases in which slight reten-	1.43	180	28	2.5
14	tion had been present a	2.07	132	34	5
15	few months earlier	1.89	145	39	2.2
16	Cases with retention	1.55	167	44	1.4
17	"	1.54	258	41	3.3
18	"	1.46	235	48	4
19	"	1.27	235	58	< 1
20	"	1.09	187	52	1.2
21	"	1.13	379	74	< 1

In a number of these cases the test was carried out on several occasions. The results on the whole were concordant, and it is not improbable that some of the slight differences in concentration found on repeating the test after an interval indicated actual changes in renal efficiency, for such differences were generally accompanied by corresponding changes in the diastatic index. In a few instances, a kidney which had previously shown good concentration yielded on re-testing an abundant urine with a low concentration, though no obvious change in the patient's condition had taken place. Without exception, however, the concentration in the cases in which urea retention was present remained low. In such cases a genuine inability to concentrate urea appeared to be present. While, therefore, a high concentration on testing appeared to indicate kidney efficiency, occasionally excessive diuresis and a low concentration were seen in cases in which the kidney function was apparently not seriously affected. This phenomenon is a result of the tendency to diuresis caused by the urea in the presence of available liquid, and may be overcome by waiting for a specimen of urine until this normal diuresis passes over. In general, if the amount of water passed per hour does not greatly exceed 100 c.c. or so, the difficulty does not arise. On the whole, since it is in practice difficult to regulate the amount of water available in the body, it is best to empty the bladder two hours after the urea is given and to examine the next specimen passed, say, in one half or one hour. Thus, if a patient gets 15 grm. of urea at 10 a.m., he should pass water at 12 a.m. If a large quantity is passed at this time and it is found to be low in urea, a further specimen should be passed about 1 p.m. This later specimen may be taken as an indication of the urea concentrating power of the kidney, since the normal

diuresis appears to be limited to the early hours after the ingestion of urea. Persistent diuresis for several hours appears to indicate defective kidneys.

*The chloride content of the urine.* It is sometimes forgotten that the function of the kidney is not restricted to the elimination of waste products. This gland fulfils another very important office in regulating the concentration of salts in the plasma. MacAllum (7) in a very interesting paper has shown that the salt content of plasma was probably determined originally by the salt content of sea-water, the medium in which all life had its origin.

Of the salts of the plasma the chlorides are the most easily estimated, and since the bulk of these salts is represented by sodium chloride the chloride content of both blood and urine is generally expressed in terms of sodium chloride. This practice is of course not scientifically correct, but gives sufficient accuracy for clinical purposes.

In certain cases of nephritis associated with oedema there is undoubtedly a tendency for the excretion of chlorides in the urine to be diminished; in some instances, indeed, they may be absent. Much discussion has taken place over the question whether this decrease in urinary chlorides is primarily due to a specific defect on the part of the kidney to eliminate salt, or whether it results from retention of water in the organism. From the practical point of view the result is the same. If we remember that any marked change in salt concentration in the fluids of the body is incompatible with life, it is evident that if the body retains fluid it will also retain salt in amount sufficient to form a solution of optimum concentration for cell activity: this concentration corresponds roughly to a 0.6 per cent. of sodium chloride solution.

If, on the other hand, salt is specifically retained, this will immediately lead to a retention of water in order to prevent excessive salt concentration in the body. It is one of the functions of the kidney to keep the concentration of chlorides in the plasma in the neighbourhood of a 0.6 per cent. solution. Unlike urea and other bodies which appear in greater percentage in the blood when the kidney fails to eliminate them, salt does not do so. In patients passing practically no salt in the urine, the blood salt concentration is little if at all higher than is the case in the healthy individual who may be passing 15 grm. per day. It is highly probable that in some conditions the kidney cells have really lost the power to eliminate chloride in the normal manner, for chloride retention is by no means always associated with a small output of water. In other cases, the phenomenon may be the result of a diminished power to excrete water, with consequent reabsorption of salt by the renal tubules. In the first case there appears to be a tendency for the patient's blood to contain chlorides in the maximum normal concentration, but such a concentration is not materially above the normal minimum concentration and may be reached by healthy individuals. Roughly speaking, the variations of salt concentration in the plasma range from about 0.55 per cent. to about 0.63 per cent.

There appears to be some evidence that a persistent low blood chloride concentration in a case of nephritis indicates primary water retention, while the



reverse condition suggests a primary salt retention. This view seems to be borne out by some experiments made by us, but we have not had sufficient cases to enable us to make any definite statement and so must leave the question an open one.

It is by no means a simple matter to determine whether a nephritic has any tendency to salt retention. The general method employed is to give a large dose of 10 to 15 gm. of sodium chloride by mouth and then estimate the amount passed in the urine. Unfortunately, such a method does not appear to give any reliable information, for, according to various investigations carried out by French observers and other authorities, the ingestion of a large amount of salt does not necessarily mean that an equivalent amount should be excreted by a healthy individual. According to Vallery-Radot (8), for instance, the amount of salt excreted after a given dose depends on the state of the tissues with regard to fluid. The amount of fluid present in the body varies considerably at different times, the actual amount perhaps depending to some extent on the quantity of sodium chloride available. If the body happens to be low in fluids the ingested salt is retained in order that the fluid may be increased, for, as already indicated, the organism requires that every 100 c.c. of retained water should contain about 0.6 per cent. of sodium chloride. Under certain circumstances salt given to a healthy subject may be eliminated to a great extent, or retained in order to increase the total amount of body fluid.

To ascertain whether or not a patient excretes salt normally, it is necessary to get salt equilibrium established by careful dietary and to follow this with large doses of salt repeated for several days. If the salt is retained an increase in weight takes place both in the healthy and diseased individual owing to the increase in fluid, but since this increase, when it takes place in the healthy subject, is limited to a few days, the former passes out in his urine in the course of three or four days an equivalent amount of salt to that taken by mouth.

On the other hand, the nephritic whose salt elimination is deficient does not respond in this way, but accumulates more and more fluid until, if the ingestion of salt is prolonged, marked oedema and ascites intervene. Since it is difficult, under ordinary conditions, to investigate the salt retention on the above lines, it is necessary to rely for information on the estimation of chlorides in the urine passed on an ordinary diet.

For the estimation of urinary chlorides Volhard's method is very satisfactory, while for the blood and ascitic fluid we have used the plan suggested by MacLean and Van Slyke (9).

## II. *The Effect of War Nephritis on Kidney Function.*

During the early stages of an acute attack of nephritis there appears to be more or less interference with the renal activity in general. Thus, in a severe case there may be marked retention of nitrogenous products in the



body with the usual abnormal ingredients in the urine: oedema more or less distinct is usually present, and the chloride content of the urine may be much diminished. Sometimes the diastatic value is very low, while in other cases it may be normal. After the first few days the condition is often succeeded by a copious diuresis by which the retained products are eliminated. In favourable cases this phenomenon is associated with a marked reduction or disappearance of oedema, and gradually the patient becomes convalescent; in course of time, varying from a few weeks to a month or two, the protein disappears from the urine and the renal function seems to be completely restored.

In other cases, however, there may be some early diuresis, but the patient does not progress very rapidly and feels unwell; on examination it is found that the blood still contains excess of urea, a condition which may persist for several months after the onset of the trouble. Such patients are often quite free from oedema and may pass only a comparatively small amount of protein in the urine, but the high blood urea figure persists, sometimes slowly decreasing and in other instances actually increasing. In such cases we have found that the diastatic reaction is of low value, and remains low for a considerable time after the blood urea has returned to normal. In some patients, on the other hand, there is no increase whatever in blood urea, and the diastatic reaction is found to be high, but the case is characterized by a persistent oedema and perhaps ascites.

From numerous investigations on cases of war nephritis which have been followed from a very early stage of the disease, it is quite certain that there are two very distinct types of the malady which can often be differentiated with certainty after the initial acute condition has passed over. As already indicated, all the kidney functions seem to be more or less in abeyance at this early stage, but this condition soon passes over, with the result that uneventful recovery may take place or a more or less tedious convalescence ensue. In the latter instance it is generally possible to divide the cases into two distinct groups in which the various tests give very different results.

In the first of these types the predominant feature is the tendency to retention of nitrogenous products (urea, &c.) in the blood. In this class of case the cardiovascular system often shows signs of degeneration: the urea concentration in the urine is decreased, and the diastatic reaction gives a low result. There is no oedema, and the urinary protein may be only moderate or slight in amount. For purposes of reference we may call this the *azotaemic* type.

In the second type the condition is markedly different. Oedema is present, and there is a tendency for the retention of chlorides. There is no retention of nitrogenous products, the diastatic reaction is high, and there is little or no cardiovascular involvement. A marked feature of this type is the large amount of protein generally present in the urine. Since its chief clinical manifestation appears to be a retention of water, and there is usually an excessive proportion of water in the blood, we will refer to this form as the *hydraemic* type.

These two types correspond in chemical findings and symptoms to the interstitial and parenchymatous forms of chronic disease, and it is interesting to

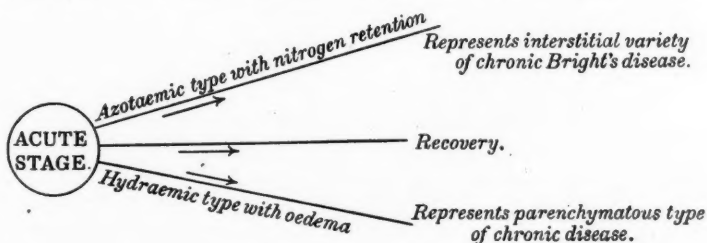
note that one or other of these types may be predominant even in acute nephritis where there is no suspicion of associated chronic disease.

There can be no doubt that the production of phenomena so entirely different in these two types indicates lesions in different parts of the renal system. Much has been written on the histological appearances of the kidneys in the different forms of chronic disease, but, unfortunately, the clinical findings so far have often not been easy to correlate with the histological changes found post mortem. Too much attention has been paid in the past to gross macroscopic appearances in the kidney. After all, it matters little whether a kidney is found to be large or small, white or red, rough or smooth, soft or hard. What is really of importance is to ascertain to what extent the kidney functions are interfered with during life, and it appears to us that little is to be gained by a more or less artificial grouping based chiefly on the naked-eye appearances of the organ after death. On the other hand, a careful attempt to correlate histological appearances with the clinical condition as indicated by chemical tests would probably give fruitful results.

Naturally we have had no opportunity of examining the kidneys of our cases for histological changes and so can furnish no direct observations on the matter, but for various reasons it appears probable that the azotaemic type is chiefly dependent on some lesion connected with the capillaries of Bowman's capsule and probably with other capillaries of the kidney, while the hydraemic variety appears to be associated with a lesion of the renal epithelium. In the first variety the essential lesion appears to be connected with the circulatory system of the kidney, while in the second the kidney cells are at fault.

In the acute case, if at all severe, manifestations of both the azotaemic and hydraemic varieties are present, since the kidney is probably suffering from a general invasion of the inflammatory process. As Auld (10) well expressed it, the kidney at this stage may be compared with a pneumonic lung. After the initial acute process has subsided the condition may entirely clear up, or convalescence may be associated with either the azotaemic or hydraemic type of symptoms or with a mixture of both.

Expressed in diagrammatic form this might be represented as follows :



Though these manifestations may be present, and yet apparently complete recovery ultimately take place, there can be little doubt that if they persist they give rise in course of time to the conditions represented by chronic interstitial and

chronic parenchymatous nephritis respectively. Of course, we are not quite certain that our apparently cured patients may not still be suffering from some defect which may reveal itself within the next few years, but so far as can be judged at present, several of these cases appear to have recovered. It is hoped that opportunities will arise in the near future to enable us to follow such cases for a number of years, so as to get information on several difficult problems of this nature. The important point, however, is that indications of the particular type of chronic disease which may ultimately develop in the event of an acute attack of nephritis failing to clear up, can be ascertained at a comparatively early stage, and while the patient is still suffering from the acute process. In fact, the nature of the subsequent development of the disease appears to be determined by the nature of the acute process, for the condition of the kidney that ultimately results in typical parenchymatous nephritis is, at an early stage of the acute process, certainly different from that which ends in chronic interstitial nephritis.

The following are the most marked differences, given in tabular form, between the hydraemic and azotaemic varieties of subacute nephritis. No doubt, in several instances, both conditions are present to some extent: in such cases one or other variety of the disease may predominate. Often, however, there seems to be a very hard and fast line between the two forms, so that a patient may show all the symptoms of the one variety without any of the conditions associated with the other type being evident.

<i>Azotaemic Form.</i>		<i>Hydraemic Form.</i>	
	(1) Oedema absent.		(1) Oedema present.
Urine.	(2) Protein present in urine, but often slight or moderate in amount.	Urine.	(2) Protein present in urine, often in very large amount.
	(3) Haematuria frequent.		(3) Haematuria absent.
	(4) Epithelial and granular casts often predominate.		(4) Small hyaline casts often predominate.
	(5) Chlorides present in normal amount.		(5) Chlorides diminished or may be absent.
	(6) Urea concentration decreased.		(6) Urea concentration normal.
	(7) Diastatic reaction low.		(7) Diastatic reaction normal or nearly so.
Blood.	(8) Tendency to increased amount of urea and other nitrogenous products in the blood.	Blood.	(8) No retention of nitrogenous products in blood.
	(9) Protein concentration often normal.		(9) Protein concentration tends to be low.
C. V. System.	(10) Heart enlarged and often tendency to arteriosclerosis.	C. V. System.	(10) Nothing marked.

The most obvious clinical difference between the two types of cases is the oedema and marked albuminuria in the hydraemic type, while the azotaemic

type shows no oedema, but is often associated with cardiovascular changes. Sometimes, as in the first case quoted below, the symptoms are more or less anomalous and cannot be brought into line with either of the two types described. This probably arises from the diffuse nature of the lesion. In the majority of cases, indications of one or other type are present, though combinations of both are not uncommon.

The following notes of cases indicate the chief chemical and clinical findings in the different types:

*Case I (Fatal Case).* Pte. M., aged 30. No previous illness. Onset 1.9.18 with general malaise and headaches. Oedema first noticed 11.9.18, and followed by vomiting and diarrhoea. Admitted with slight oedema of thighs and lumbosacral region and moderate ascites. He was at this time somewhat drowsy, and occasional facial twitchings were noticed. No thickening of radial vessel. Blood-pressure (systolic) 131 mm. Hg. Apex beat in left nipple line. Urine smoky, with much albumin. Occasional hyaline casts with numerous leucocytes, epithelial cells, and red blood corpuscles. The course of the case was steadily downhill, with repeated epistaxis, a subnormal temperature, vomiting, and diarrhoea. He died on 2.11.18.

In the following table the amount of urine and its urea concentration for the hour during which the blood sample was taken is given along with the blood urea and diastatic index of the urine.

Date.	Blood Urea in mg. per 100 c.c.	Urine Urea %.	Amount of Urine in c.c.	Diastatic Index.
17.9.18	249	—	—	—
25.9.18	331	0.91	31	2.8
1.10.18	380	0.99	20	2.8
5.10.18	461	1.14	35	4
11.10.18	530	1.11	47	3.3
21.10.18	592	1.20	75	10

A very marked inability to concentrate urea was obviously present, the urinary concentration being only two or three times that of the corresponding blood sample, while the figure for the normal individual usually amounts to more than fifty times the blood urea value. In the later stages the daily excretion of urine rose considerably, possibly owing to the diuretic action of the high blood urea, and at times as much as 2,000 c.c., containing 20 gm. of urea, were passed per day. At the time of his death the patient was free from oedema. In spite of the steady deterioration of his condition, the urinary diastatic index rose considerably, probably as the result of a rise in the diastatic index of the plasma from 10 to 28.

*Cases of Azotaemic Type showing Prolonged Nitrogenous Retention in the Blood with or without a return to Normal Limits.*

*Case II.* Pte. K., aged 45. Onset 4.8.18 with oedema preceded by shortness of breath and orthopnoea. Admitted to Field Ambulance 6.8.18. Total duration of oedema fourteen days. On admission to hospital no oedema. Radial slightly thickened. Apex beat internal to left nipple line. Urine smoky. Albumin marked. Fair numbers of epithelial and some hyaline casts. Macroscopic blood present until 21.11.18. On discharge apex beat in nipple line. Blood-pressure  $188/2$ . Radial vessel definitely thickened. Occasional headaches. Urine contained a faint trace of albumin and an occasional granular cast with a few red blood cells.

Some of the findings in this case are given in the table.

Date.	Blood Urea in mg. per 100 c.c. Blood.	Diastatic Value.	Urea Concentra- tion after 15 gm. Urea.	Amount of Urine in c.c. passed during 2 hours of Urea Test.
23.9.18	51	3.3	—	—
3.10.18	73	2	—	—
25.10.18	60	2	—	—
21.11.18	52	1.5	1.09	187
13.12.18	56	less than 1	0.99	226
23.1.19	43	1.2	1.21	241

*Case III.* Pte. B., aged 33. Onset 14.8.18, with shortness of breath followed by oedema and headaches. Oedema lasted only five days.

On admission to hospital, no oedema. Radial slightly thickened. Apex beat in left nipple line. Systolic blood-pressure 118 mm. Hg. Urine smoky. Much albumin with numerous casts, mainly hyaline and hyalo-granular with some epithelial. Macroscopic blood present in urine until 23.12.18.

On discharge radial was slightly thickened. Apex beat in the nipple line. Blood-pressure  $124$ . Nocturnal frequency of micturition. Urine clear. Albumin faint trace. A few hyaline and epithelial casts present.

Date.	Blood Urea in mg. per 100 c.c. Blood.	Diastatic Value.	Urea Concentration Test.
23.9.18	65	less than 1	—
2.10.18	109	" 1	—
17.10.18	101	" 1	—
4.11.18	94	" 1	—
19.11.18	58	" 1	1.27 % (234 c.c. urine)
7.12.18	47	" 1	1.30 % (267 c.c. urine)
23.1.19	36	2	1.37 % (217 c.c. urine)

*Case IV.* Pte. S., 35 years of age. Shortness of breath noticed on 26.7.18. On 4.8.18, oedema with headache and vomiting. Admitted to Field Ambulance 8.8.18. Oedema disappeared on 10.8.18.

On admission to hospital there was no definite radial thickening. Apex beat external to left nipple line. Systolic blood-pressure 134 mm. Hg. Urine smoky, with a moderate amount of albumin and fair numbers of epithelial and some hyaline casts. Occasional headaches. Macroscopic blood persisted in the urine until 26.11.18. Apex beat on discharge (6.2.19) was one-quarter of an inch external to the left nipple line with a rumbling first sound at the apex. Blood-pressure  $149$  mm. Hg. Radial definitely thickened. Urine contained a faint trace of protein with some granular and hyaline casts. Polyuria was present.

Date.	Blood Urea in mg. per 100 c.c. Blood.	Diastatic Value.	Urea Concentration Test.
13.9.18	31	3.2	—
3.10.18	67	2.2	—
25.10.18	96	less than 1	—
14.11.18	74	" 1	1.13 % (379 c.c. urine)
4.12.18	62	" 1	—
20.12.18	46	" 1	1.12 % (191 c.c. urine)
24.1.19	37	" 1	1.19 % (623 c.c. urine)

*Case V.* Cpl. H., aged 28. Onset 1.9.18 with shortness of breath, followed by oedema and headache. Immediately before admission to hospital he had two severe malarial rigors. On admission he was very anaemic, with slight oedema of the ankles and slightly thickened radial. Apex beat in left nipple line. Systolic



blood-pressure 99 mm. Hg. Spleen palpable. Urine deeply smoky, with moderate amount of albumin and numerous granular casts and some red-blood cells.

Oedema cleared on 30.9.18. Macroscopic blood in the urine until 18.11.18.

On discharge (1.2.19) the apex beat was internal to the nipple line. Blood-pressure  $\frac{120}{73}$ . Urine was free from albumin, and only a few hyaline casts were seen.

Date.	Blood Urea in mg. per 100 c.c. Blood.	Diastatic Value.	Urea Concentration Test.
25.9.18	209	less than 1	—
1.10.18	71	" 1	—
8.10.18	37	3.3	—
21.10.18	47	5	—
8.11.18	41	1.4	1.55 % (258 c.c. urine)
6.12.18	29	2	1.55 % (236 c.c. urine)
27.1.19	31	10	2.02 % (222 c.c. urine)
30.1.19	—	6.6	—

In these last four cases the blood urea slowly returned to a concentration approximating the normal. This diminution in the blood urea concentration was accompanied by an increase in the daily urinary measure, but the urea concentration in numerous samples tested remained low. In Cases III and IV, the fall of urea in the blood was probably quickened by an increase in fluid ingestion—these two patients receiving about 3,000 c.c. fluid daily for a considerable period. In the first three cases of the azotaemic type it will be noticed that though the blood urea fell, the concentration with the urea test remained low, and there was no marked rise in the diastatic index. In these patients evidence of arterial changes was present on discharge, and in two of them cardiac hypertrophy and a raised blood-pressure were also found. The disappearance of nitrogenous retention probably indicated the attainment of compensation, but by no means a complete recovery of kidney efficiency.

In Case V evidence of improvement accompanied the fall of blood urea as indicated by a rising diastatic and an increased capacity for concentrating urea. This is a good example of a case in which recovery, though very delayed, ultimately takes place.

#### *Cases of the Hydraemic Type.*

*Case VI.* Pte. R., aged 41. Onset with headaches on 14.8.18, followed by oliguria, and on 14.9.18 by oedema.

Admitted to hospital on 4.10.18 with oedema of back and ankles. Radial vessels not thickened. Apex beat just internal to left nipple line. Blood-pressure  $\frac{108}{68}$  mm. Hg. No macroscopic blood in urine. Albumin very pronounced, and considerable numbers of hyaline and hyalo-granular casts with a few epithelial present. The oedema was still present on discharge on 7.2.19, and at times ascites could be demonstrated. The urinary condition remained unchanged and no cardiovascular changes were noticed. Blood-pressure on discharge  $\frac{126}{82}$ .

Date.	Blood Urea in mg. per 100 c.c. Blood.	Diastatic Value.	Urea Concentration Test.
4.10.18	36	6.6	—
17.10.18	29	10	—
13.11.18	24	10	2.38 % (100 c.c. urine)
2.12.18	—	1.6	—
3.12.18	57	5	1.07 % (163 c.c. urine)
10.12.18	38	6.6	1.82 % (237 c.c. urine)
16.1.19	26	10	—



In this patient the blood urea concentration was within normal limits, except on 3.12.18, when it rose to 57 mg. apparently as the result of some condition which caused the appearance of a patch of consolidation in the left lung with an initial rigor followed by three days' pyrexia. At the same time, as indicated in the above table, there was a marked fall in the diastatic and a lowered concentration with the urea test. The appearance of the increased urea percentage in the blood was followed by a transitory diuresis, as much as 3,600 c.c. of urine being passed in one day. This, however, ceased with the return of the blood urea to normal limits, and was not sufficiently prolonged to clear the patient entirely of oedema. A high degree of albuminuria persisted throughout the patient's stay in hospital, but no blood was ever found in the urine. Cardiovascular changes were absent, and the diastatic index remained high.

In a similar type of case with persistent oedema, ascites, and marked albuminuria, but no cardiovascular changes, the following were the findings:

Date.	Blood Urea in mg. per 100 c.c. Blood.	Diastatic Value.	Urea Concentration Test.
30.8.18	34	10	—
15.9.18	27	6.6	2.37 % (146 c.c. urine)

In both the above cases the urinary chlorides were much diminished.

The following two cases may be regarded as instances of the mixed type:

*Mixed Type of Case with Azotaemic and Hydræmic Symptoms.*

*Case VII.* Pte. G., aged 48. Onset on 1.7.18 with oedema and shortness of breath. Admitted to Field Ambulance 14.9.18, and to this hospital on 24.9.18. On admission there was considerable oedema of the back, thighs, and ankles, with basal pulmonary oedema and ascites. Radial artery moderately thickened. Apex beat just external to the left nipple line. Blood-pressure  $\frac{156}{94}$ . The urine contained much albumin and fair numbers of hyaline, hyalo-granular, and epithelial casts. The oedema steadily persisted until 18.11.18, when it finally cleared up on drastically reducing the patient's salt ration. From 14.10.18 to 23.10.18 macroscopic blood was present in the urine. Slight oedema recurred at the end of December. On discharge the blood-pressure was  $\frac{145}{88}$ , the urine containing considerable amounts of albumin and fair numbers of hyaline and granular casts, with an occasional epithelial cast.

The course of this case is indicated in the following table.:

Date.	Blood Urea in mg. per 100 c.c. Blood.	Diastatic Value.	Urea Concentration Test.
25.9.18	264	6.6	—
1.10.18	151	6.6	—
8.10.18	118	10	—
14.10.18	62	10	—
21.10.18	57	6.6	—
4.11.18	70	10	—
19.11.18	48	4	—
10.12.18	38	1.5	1.46 % (235 c.c. urine)
21.1.19	32	2.2	1.37 % (184 c.c. urine)
21.1.19	—	4	1.41 % (252 c.c. urine)

*Case VIII.* Pte. M., aged 41. Oedema, headache, and shortness of breath developed on 12.8.18. He was admitted to this hospital on 25.8.18 with moderate oedema of back and ankles. Radial slightly thickened. Apex beat internal to left nipple line. Systolic blood-pressure 145 mm. Hg. Urine contained much

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albumin and numerous hyaline, hyalo-granular, and epithelial casts. Oedema persisted until 29.10.18, and disappeared after markedly reducing his salt ration. From 12.10.18 to 29.10.18 the urine was smoky. He was discharged on 1.2.19 with evidence of slight cardiac hypertrophy, slight trabecular thickening, and a blood-pressure of 145 mm. Hg. The urine was then free from blood, but showed a very considerable amount of albumin and some hyaline epithelial casts.

Date.	Blood Urea in mg. per 100 c.c. Blood.	Diastatic Value.	Urea Concentration Test.
31.8.18	56	3.3	—
2.10.18	37	4	—
14.10.18	33	4	—
13.11.18	28	4	1.43 % (180 c.c. urine)
16.12.18	34	2.5	1.33 % (153 c.c. urine)
16.1.19	34	2.3	1.85 % (158 c.c. urine)

In both these cases there was initial urea retention, in one case prolonged with a falling diastatic index. The concentration with the urea test was on the low side, and cardiovascular changes with occasional haematuria were present. At the same time the ability to excrete chlorides was impaired and the prolonged oedema only cleared on strictly limiting the ingestion of salt. Persistent oedema and marked albuminuria which does not tend to clear up readily differentiates these cases from the pure azotaemic type.

A few instances may be given of milder cases in which there was not apparently at any time any severe defect in the excretory function of the kidney while under our observation, and in which on discharge renal efficiency seemed to be good.

*Examples of Milder Cases in which Kidneys seemed efficient..*

*Case IX.* Pte. B., aged 42. Onset with oedema of six days' duration on 28.8.18. Slightly thickened radial. Apex beat in left nipple line with a blowing systolic murmur. Blood-pressure 118 mm. Hg. Urine contained a moderate amount of albumin with numerous hyaline and hyalo-granular casts. Discharged 29.1.19 with a faint trace of albumin and a few hyaline casts. Blood-pressure  $\frac{121}{71}$ .

Date.	Blood Urea in mg. per 100 c.c. Blood.	Diastatic Value.	Urea Concentration Test.
19.9.18	28	4	—
17.10.18	32	5	—
13.11.18	30	6.6	2.14 % (147 c.c. urine)
27.1.19	37	6.6	2.37 % (135 c.c. urine)

*Case X.* Pte. D., aged 26. Onset with headache, shivering, and probably haematuria on 14.7.18. On admission to this hospital no oedema or cardiovascular changes. Urine contained a small amount of albumin with some epithelial and hyaline casts. No macroscopic blood. On discharge on 26.1.19 no cardiovascular changes. Blood-pressure  $\frac{128}{80}$ . Urine contained a trace of albumin with a few hyaline casts and an occasional epithelial cast.

Date.	Blood Urea in mg. per 100 c.c. Blood.	Diastatic Value.	Urea Concentration Test.
16.9.18	41	10	—
28.10.18	28	4	—
25.11.18	34	5	2.07 % (132 c.c. urine)
12.12.18	32	5	2.20 % (136 c.c. urine)
24.1.19	32	6.6	2.79 % (130 c.c. urine)

*Case XI.* Pte. M., aged 20. Onset 19.8.18 with oedema which lasted three days' only. On admission to hospital no definite cardiovascular changes. Blood-pressure 102 mm. Hg. Urine was smoky, with a small amount of albumin and a fair number of epithelial and small granular casts. Haematuria lasted for three days after admission. On discharge on 20.12.18 the urine was free from albumin and casts.

Date.	Blood Urea in mg. per 100 c.c. Blood.	Diastatic Value.	Urea Concentration Test.
10.9.18	20	10	—
5.10.18	36	6.6	—
15.11.18	24	5	2.67 % (127 c.c. urine)
18.12.18	23	10	2.74 % (124 c.c. urine)

*Case XII.* Pte. L., aged 34. Onset with shortness of breath on 18.7.18. Oedema 1.8.18, with vomiting, headache, and oliguria. Admitted to Field Ambulance on 8.8.18. Oedema subsided in three days. On admission to hospital, cardiovascular system appeared to be normal. The urine contained a trace of albumin and a few hyaline casts.

Date.	Blood Urea in mg. per 100 c.c. Blood.	Diastatic Value.	Urea Concentration Test.
10.9.18	20	10	—
4.10.18	24	10	—
12.11.18	27	10	2.07 % (121 c.c. urine)
12.12.18	—	10	2.42 % (140 c.c. urine)

In these cases the attack seems to have left little, if any, impairment of renal function. No increase of blood urea was observed, the oedema was of short duration, cardiovascular changes were absent, the diastatic index approximated the normal, and haematuria, if present, was of short duration. The ultimate chemical findings were also satisfactory.

### III. Observations on Treatment.

The active treatment of acute nephritis reduces itself largely to the treatment of symptoms, and with this we are not concerned here. The principle, however, is generally accepted that a low protein diet is indicated in the early stages, especially in cases in which there is a retention of nitrogenous products. Very often this low protein diet is regulated according to the amount of protein appearing in the urine, so that in certain cases it is the practice of medical men to persist with it for long periods. Often milk is made use of in this connexion, and it is not infrequently forgotten that milk is a form of food comparatively rich in proteins. On general principles it is probably correct treatment to give low diets, especially as regards protein, during the early stages of the malady; but it is by no means certain that protein does any harm, especially during the subacute and convalescent periods of the disease. Though it is often enough inferred in the literature that an increase in protein intake tends to raise the total percentage of protein in the urine, we have obtained little evidence of this in our cases. In the urines of several patients examined by us, little or no increase in the urinary

protein could be ascertained after protein meals, and we are inclined to think that if this alleged increase in albuminuria after ingestion of protein takes place at all, it is a much rarer phenomenon than is generally supposed.

On physiological grounds it is difficult to understand why protein, which according to modern teaching is hydrolysed in the intestine and resynthesized by the tissues from the amino-acids in the blood, should increase the protein of the urine. No doubt, it is a difficult question to decide whether or not a large protein meal immediately increases the blood protein, but if it does so at all it can only do it to a very slight extent if we accept as correct the modern ideas on protein metabolism. Indeed, so far as the evidence goes, it would appear that blood protein is only slowly built up, just as is the case in other tissues. The point to be noted is that protein is essentially different from such a substance as sugar which is absorbed as such into the circulation, and tends to increase directly the blood sugar concentration.

Further, there is no evidence that protein causes any injurious effects in the type of renal disease in which there is no tendency to nitrogenous retention—the hydraemic type. Indeed, we really do not know whether protein in ordinary amount does harm even in azotaemic cases where there is a tendency to nitrogenous retention, but in the present state of our knowledge it seems wise, on general principles, to enforce certain restrictions as regards protein in such patients. It must, however, be borne in mind that patients suffering from subacute nephritis should have a sufficient amount of food, for the detrimental effect of an insufficient diet retards progress. In the two different types of nephritis, however, modifications in the dietetic treatment are indicated. With regard to water it was our custom to give unlimited amounts to the azotaemic type of patients during the subacute stage, and even to encourage drinking. In the hydraemic variety the intake of fluids was naturally kept moderately low.

*Diet in the azotaemic type.* In the azotaemic type of nephritis we have proceeded on the principle that a low diet is indicated during the acute stage, and that this should be followed, at least for some time, by a diet of reduced protein content but rich in carbohydrates and fats. Sometimes such a diet may give rise to digestive disturbances, but this is rare. After a month or two, depending on the severity of the case, all our patients were put on ordinary hospital diet.

*Diet in hydraemic type.* In the hydraemic case, after the acute stage is over, the conditions are entirely different. Here there is no tendency to retain nitrogen, and no apparent reason exists why protein should not be given in the usual amount. Since this type of case corresponds to the chronic parenchymatous variety, we have adopted in our hydraemic cases the method of dietetic treatment recommended by Epstein (11) in parenchymatous nephritis. In this condition, in which one of the most trying symptoms is pronounced oedema often accompanied by ascites, Epstein found that feeding with a diet of very high protein content often resulted in a decrease or removal of the dropsy. This beneficial result he ascribed to an increase in the protein of the blood plasma.

In these cases there is generally a large amount of protein lost in the urine, and Epstein concluded that this drain of protein resulted in a low protein concentration in the blood, which lowered the plasma osmotic pressure to such an extent that water escaped from the blood-vessels into the tissues. The increased protein diet, by raising the plasma protein content, augmented the power of the plasma to retain water in the blood-vessels and so prevented an accumulation in the tissues. The water retained in the blood was of course thrown off by the kidneys instead of being passed on to the tissues.

That a high protein diet often results in removal of the dropsy in chronic parenchymatous nephritis is certain, but the cause of this is not very easy to ascertain with certainty. While increase of plasma protein may be a factor in some cases, it is certainly not the essential one, for we have seen a case, in which the oedema and ascites were exceedingly severe, clear up in two months without any increase of the protein in the blood. Particulars of this case are given below (Table III). Here it will be seen that the blood protein remained practically constant; indeed, if anything, it showed a slight tendency to decrease. This patient suffered from ascites so pronounced as to necessitate tapping every two weeks. At each tapping from 8 to 12 pints of fluid were removed; oedema was also extreme, and for over six months the patient had been bedridden.

The urine contained only the faintest trace of chlorides.

On October 14, 1918, he was put on the high protein diet recommended by Epstein. For some little time his condition remained unchanged, but gradually during the next three months his daily output of urine rose from an average of 20 to 25 ounces to a maximum of 80 to 100 ounces. He was tapped on November 15 and on December 6, when 12 and 10 pints of fluid respectively were removed. Since his last tapping, now over six months ago, he has been free from ascites and oedema, has put on flesh, and looks and feels much better. The renal condition is, of course, not cured, for he still continues to pass large amounts of albumin (from 12 to 20 gm. per day), but his general physical comfort is increased to such an extent that life, which was formerly so trying for him, is now comparatively pleasant. On his present diet he is passing from 2 to 3 gm. of chlorides per day.

A case very similar to the above has recently been described by Clifford Allbutt (12).

TABLE III.

*Details of Blood Protein and Urea in above Case.*

Date.	Protein in Plasma.	Urea in Blood.
October 13, 1918	6.29 %	27 mg. per 100 c.c.
November 20, 1918	6.20 %	64 "
December 3, 1918	6.00 %	56 "
January 3, 1919	—	81 "
January 22, 1919	5.96 %	63 "

*The effect of urea in causing diuresis in nephritis.* Since the protein content of the plasma of this patient tended rather to decrease than increase, it is certain



that, in this instance at any rate, Epstein's explanation does not hold. What then could have been the cause of the marked diuresis by which the waterlogged cavities and tissues were drained? We are inclined to think that the explanation lies in the increase of blood urea consequent on the enhanced protein diet. Urea acts normally as a powerful diuretic in cases where there is available fluid for excretion, and has been credited with results in parenchymatous nephritis where other diuretics have failed to act (13). From an initial value of 27 mg. per 100 c.c. of blood the urea rose to a maximum of 81 mg., being generally in the neighbourhood of 60 mg. Now this amount of urea should be sufficient to stimulate marked diuresis, and in order to test this we tried the effect on a similar case of continuous doses of urea given by mouth. Here, again, the quantity of urine was more than doubled, though other diuretics had little effect. Unfortunately, this patient refused to continue taking the urea owing to its unpleasant taste and its tendency to cause sickness; it was obvious, however, that the treatment had resulted in a reduction of the dropsy.

In still another patient suffering from the hydraemic variety of war nephritis with persistent oedema, a slight pulmonary complication ensued accompanied by a temporary urea retention in the blood. Here the urea rose from 24 mg. to 57 mg. Three days afterwards a copious diuresis occurred, and continued until the blood urea content reached normal, the result being that the original troublesome oedema was much decreased.

This effect of urea probably explains the cause of the marked diuresis so often seen in acute nephritis after the first few days. In these cases there is a tendency for the retention of the urea, water, and other ingredients. The urea content of the blood increases and the tissues contain an excess of water. Soon the kidney recovers somewhat from the original inflammatory invasion and the renal cells begin to functionate more normally. Here, then, we have all the conditions making for a profound diuresis—an increased blood urea content, excess of water in the tissues, and a recovering kidney.

The consequence is that in ordinary cases diuresis goes on until the oedema disappears, or until the blood urea returns to its normal level. Indeed, it would seem as if the storing up of urea acts as a provision of Nature to ensure the rapid removal of retained fluid.

In chronic parenchymatous nephritis there is no tendency to retain urea while the patient is on ordinary protein diet, but on a much increased diet, such as that recommended by Epstein, the blood urea concentration is appreciably increased, with the result that diuresis follows. Whether or not this is the full explanation of the phenomenon, there is little doubt that it plays an important part.

If we accept the teaching that a large amount of protein food is indicated in parenchymatous nephritis with dropsy, we are confronted with the apparently anomalous principle that in cases where there is much albuminuria (nearly always parenchymatous cases) the larger should be the amount of protein given in the food. This is, however, quite reasonable on various grounds, since the



actual daily loss of protein by the urine is very appreciable and some attempt should be made to compensate the body for this loss. Also, if the increase in blood urea is the chief or only factor in the causation of diuresis, it is much more pleasant to induce the condition by means of protein food than by the more direct but unpleasant method of giving urea by mouth.

The withholding of salt is also of much value in certain mild hydraemic cases, for in several of our patients oedema persisted as long as the ordinary amount of salt was permitted in the diet, but rapidly subsided on cutting off salt. In cases of severe parenchymatous dropsy, however, a so-called salt-free diet often fails to have any appreciable effect.

#### *IV. Discussion of Tests for indicating Kidney Efficiency.*

The question of the efficiency of the kidney in patients with subacute and chronic nephritis is of great importance, especially at the present time, when so many men are suffering from the effects of war nephritis. That the presence of albuminuria does not afford much help is obvious, when we consider that over 5 per cent. of the apparently fit men on active service had some albumin in their urine and that 2 per cent. of these had gross albuminuria (14). Further, the extent of the albuminuria is of little value as an index to the gravity of the case, for it is well known that the more serious cases may show but traces of albuminuria. In general, the amount of protein in the urine in subacute and chronic cases is probably of more importance in indicating the predominating type of disease present than in furnishing information as to the gravity of the renal condition.

In the early stages of an acute attack of nephritis the blood urea content furnishes the best indication of the state of the kidney. If, this is normal, it may, be taken for granted that the damage to the kidney is not sufficient to interfere with its normal function of excreting nitrogenous products. If, on the other hand, the blood urea figure is high, the most valuable information as to the progress of the disease is obtained by occasional estimations of blood urea. If the urea tends to get less, the prognosis is good; if it gets persistently higher, the outlook is correspondingly bad. In severe chronic interstitial conditions the same state of affairs is present.

In many subacute and chronic conditions the kidney is not sufficiently damaged to cause an increase in blood urea, and so no information is to be obtained by this test. In such cases other means must be employed, and we have found that the capacity of the kidneys to concentrate urea in the urine, under the conditions already fully described, affords very helpful information. If, after receiving 15 grm. of urea by mouth, the patient excretes urine containing 2 per cent. or so of urea, it is safe to conclude that the kidney is at least fairly efficient. If the urine concentration is low, it is in the great majority of cases an indication that the kidney is inefficient. As already mentioned, it sometimes happens that the normal diuresis caused by urea tends to give a urine of low urea concentration in a healthy subject, but this difficulty can be overcome by

discarding the specimens of urine passed during the first two or three hours after the administration of the urea and examining a later specimen. In conjunction with the above test the estimation of the diastatic index is of great value. Usually the indications given by both tests agree, and when one goes down the other also decreases, and vice versa. In cases where functional tests such as the above indicate that the renal function is being efficiently carried out, it is important to investigate the condition of the cardiovascular system, for the indirect danger of cerebral haemorrhage or cardiac failure may be much greater than any direct manifestation arising from kidney inefficiency.

Besides the above methods we have used several other tests from time to time. Of the various dyes used in this connexion the most popular at the present time is phenolsulphonphthalein. This dye seems to give a very good indication of the state of the kidney function in general, but, in our experience, fails to differentiate between the different types of nephritis. When the kidneys are capable of secreting from 40 to 50 per cent. of the dye in one hour, there is probably not much disturbance of function, but it appears to us that the test is not sufficient by itself to give the required information in the absence of other methods of investigation. In conjunction with other tests it is undoubtedly of much value.

Finally it is most important to emphasize that, whatever the result of the various functional tests may be, no prognosis should be given without first carefully examining the state of the cardiovascular system.

## REFERENCES.

1. MacLean, F. C., *Journ. Exper. Med.* 1917, xxvi. 181.
2. Hewlett, Gilbert, and Wickett, *Archiv Int. Med.*, Chicago, 1916, xviii. 636.
3. Van Slyke and Cullen, *Journ. Biol. Chem.*, Baltimore, 1914, xix. 219.
4. Wohlgemuth, *Biochem. Zeit.*, Berlin, 1908, ix. 1, and 1909, xxi. 381.
5. Corbett, *Quart. Journ. Med.*, Oxford, 1912-13, vi. 351.
6. De Wesselow and MacLean, H., *Reports of the Committee on War Nephritis*, No. 3, II, June 1918.
7. MacAllum, A. B., *Trans. Coll. Physicians*, Philadelphia, 1917, xxxix. 7.
8. Vallery-Radot, *Études sur le Fonctionnement rénal dans les Néphrites chroniques*.
9. MacLean, F. C., and Van Slyke, *Journ. Biol. Chem.*, Baltimore, 1915, xxi. 361.
10. Auld, *Brit. Med. Journ.*, 1917, ii. 414.
11. Epstein, *Amer. Journ. Med.*, 1917, N. S., cliv. 638.
12. Clifford Allbutt, *Brit. Med. Journ.*, 1918, ii. 395.
13. Cushny, *The Secretion of the Urine*, Lond., 1917.
14. MacLean, H., *Brit. Med. Journ.*, 1919, i. 94.

AN INVESTIGATION ON FATAL CASES OF PERNICIOUS  
MALARIA CAUSED BY *PLASMODIUM FALCIPARUM*  
IN MACEDONIA

By LEONARD S. DUDGEON AND CECIL CLARKE

With Plate 23

THE presence of British troops in Macedonia during the year 1917 has afforded further opportunity to study the lesions of fatal malaria. Dudgeon and Clarke (1) in a previous communication, based on a study of a limited number of cases during 1916 and the early period of 1917, gave a summary of the microscopic findings in the important viscera, but referred more especially to fatty degeneration of the cardiac muscle. In the main the lesions enumerated were largely a repetition of the classical observations of the pioneers in this important branch of tropical medicine.

During the season of 1917 the material has been collected with the definite object of correlating, as far as possible, the clinical history with the microscopical examinations. In the first place, it is to be regretted that active service conditions do not permit invariably of as full a clinical history as is desirable. Moreover, it is inevitable that a certain proportion of cases come under observation already in a state of coma or grave collapse and a detailed previous history is unobtainable. On the other hand, the microscopical investigation has been sufficiently complete for this purpose in fifty cases.<sup>1</sup> The lack of some essential tissue, usually the brain, has prevented the inclusion of a further nine cases in any special group, but the results available are included in the general survey.<sup>2</sup>

The majority of cases came from troops occupying the Doiran-Vardar sector, dying in the casualty clearing stations corresponding to that area. Mention is made of this point, as it may seem that the number of cerebral cases is large. Of necessity it included those who were so seriously ill as to be unable to be evacuated to the base, a high proportion dying within twenty-four hours of admission to hospital.

<sup>1</sup> Many observations derived from a study of certain tissues apart from a complete survey of the cases are included here.

<sup>2</sup> Further observations on the tissue changes in chronic malaria associated with grave anaemia will be published later.

It was observed that the examination of the peripheral blood did not of necessity indicate the gravity of the clinical condition of the patient. A high percentage infection of the red cells may be compatible with a mild attack of malaria which readily responds to treatment. On the other hand, it has been not an uncommon experience to find, and only after prolonged search, a few parasites in the peripheral blood of a patient who presents the features of a severe attack of malaria which may terminate fatally. Microscopic examination of the tissues may show numerous infected red corpuscles and the vessels blocked with these cells.

*Technique.* All sections were stained with haematoxylin and eosin, while Scharlach R. was employed to demonstrate fats and fatty substances. Van Gieson's, Nissl's, Marchi's, Leishman's, and Giemsa's methods were adopted whenever necessary. The presence of free iron was determined by immersing the sections in a mixture of 25 per cent. hydrochloric acid in 75 per cent. alcohol and 2 per cent. aqueous solution of ferrocyanide of potassium for thirty minutes at 37° C. Other stains were employed for special purposes.

#### *Classification of Cases.*

As a basis for classification of the cases, we have relied on the microscopical examinations of all the important tissues, and where local massing of parasites or important pathological changes have been demonstrated in any given organ, such cases are included under that heading. A certain amount of overlapping of those cases which show lesions referable to one or more of the viscera is unavoidable in a disease with such widespread manifestations as acute malaria, but the arrangement is convenient for the purpose of correlating in certain instances the clinical and pathological observations.

In this paper we wish to draw attention especially to certain changes induced by the malarial parasites, e.g. fatty degeneration of the heart muscle, haemorrhages into the lung alveoli, and also to discuss the rôle of the suprarenals in death from pernicious malaria.

#### *Morbid Anatomy.*

The post-mortem appearances of acute malaria are too well recognized to warrant any detailed description. With regard to the microscopic appearance of a brain which on microscopic examination shows blocking of the capillaries, it has been recorded that the grey matter presents a characteristic leaden hue or discoloration. The brain is from a case which on section showed complete obstruction of the capillaries and arteries infected with red cells and melanin. The numerous obstructed blood-vessels outline the arterioles and venules of the central and cortical branches of the anterior, middle and posterior cerebral arteries. Examination with a hand lens will suffice to demonstrate a blocking of the small vessels, but for the finer grades of capillary obstruction microscopic examination is necessary.

The clots cannot be removed from the interior of the vessels in such cases without considerable difficulty, as they are firmly adherent to the vessel walls, in contrast to the apparent obstruction so commonly seen in the cerebral vessels in malarial fever. The adherent clots consist mainly of infected red cells, free parasites, melanin, and large endothelial cells.

Another appearance worthy of notice is the loss, partial or complete, of the normal yellowish colour of the cortex of the suprarenals, consequent on the disappearance of 'lipoids' and fats; microscopical examination invariably confirmed this observation.

No alteration of the appearance of the cardiac muscle beyond occasional apparent congestion, varying degrees of flabby musculature, and lesions unrelated to the malarial process, was recognized. In one case the left auricular vein was thrombosed, its course outlined by large subpericardial petechial haemorrhages.

The splenic enlargement was constant, the average weights in one series of post-mortems varying from 280 to 450 grm.; the highest weight in a chronic case was 960 grm.

Confronted as one was not infrequently during two seasons with the problem of a man found dead, or who had died suddenly, with no details of previous history obtainable or record of blood-film examination, the comparatively meagre morbid appearances were disappointing. While the immediate diagnosis of malaria could be confirmed by the spleen smear, the actual determining cause of the fatal issue could not be made without a complete microscopical examination.

#### *Cerebral and Comatose Group.*

It has been customary in describing the several phenomena of the pernicious access in malaria to separate certain clinical types of disease, e. g. the cerebral group with many subdivisions, the pulmonary and renal, &c. Such classifications are of advantage only in emphasizing the important complications and in compelling our attention to be focused on a special organ by reason of the clinical features of the case.

The fundamental conception of the pathogenesis of the pernicious access is the local massing of malaria parasites, often in enormous numbers in certain tissues, notably the brain, occasionally the intestine. This conception affords us a correct explanation, for example, of most instances of cerebral malaria, but does not hold good for all cases.

From the pathological standpoint there are three groups, possibly more, of the 'comatose' type, (1) referable to effects of massing of parasites and pigment in the cerebral capillaries, (2) referable to punctiform haemorrhages into the cerebral tissues. Both these changes may be seen in the one case. A third variety described in the literature is attributed to emboli of parasites and pigment. There still remains another group in which no determining lesion has been found in the brain or any of the other viscera examined.

From a study of sixty-four cases of malarial coma at Montauk and New



York, Ewing (2) considered that this cerebral symptom occurred in three rather distinct clinical pictures and under three entirely different pathological conditions. We refer somewhat fully to these remarks and contrast the findings with those obtained in Macedonia.

*Type 1*, referable to massing of young amoeboid parasites in the cerebral capillaries.

'Clinically, the coma resulting . . . is rather slowly established in the course of active infections, when many young parasites are found in the finger blood<sup>3</sup> and when the temperature is elevated. The patient is usually first delirious, then mildly comatose, then deeply comatose, finally stuporous, with abolition of pupillary and other reflexes, and almost always dies within forty-eight hours after the beginning of marked cerebral symptoms. Of eleven such cases observed at Montauk ten died, and very vigorous treatment succeeded in saving only one.' The deepening stages of the coma could be connected with the increase in size of the parasites and gradual filling of the vessels with thrombi of infected red cells, pigmented leucocytes, and swollen endothelial cells.

Our results in twenty-one cases are in close agreement with those of Ewing's.

#### *Summary.*

(a) *Clinical.* Twenty-one cases dying in coma showed massing of numerous malarial parasites in the cerebral capillaries. Every case was energetically treated with quinine either by the intramuscular or intravenous routes, usually both, from the time of first coming under medical observation.

The onset of such cerebral symptoms as drowsiness, mild delirium, apathy, restlessness, was noted as gradual in twelve. Of the remainder, nine, when first seen, were already deeply comatose, and no other history is available. In these it is at least probable that the onset of coma was sudden or deepened rapidly. Usually the notes indicate a gradual progression from mild to deep coma. In twelve cases from the onset of the first important cerebral symptom, the end was fatal in twenty-four hours or less. The most rapid termination was six hours (one case) and the longest duration sixty hours (two cases).

The temperature, where such record exists, was raised invariably, 100° to 105° F. The evidence at our disposal does not permit of the expression of any opinion as to the correlation of the increase in size of the parasites with the deepening of the coma, as Ewing observed in his cases.

(b) *Microscopic.* The capillaries, and in the most severe cases the arterioles, were engorged with numerous infected red blood cells which showed the well-known tendency to collect at the periphery of the vessels, free parasites, melanin particles, prominent and detached endothelial cells. Various phases of development were represented, 'dot' forms, fine rings, segmenting forms, but crescents

<sup>3</sup> Words are underlined by us as they do not invariably represent the findings in Macedonia.



were not seen. All gradations of blocking up to complete thrombosis with agglutination of and altered staining reactions of the corpuscles were exemplified. The distribution of parasites was as a rule quite uniform throughout the sections examined, but in two instances the changes in the cerebellum were more obvious than in the cerebrum.

Small haemorrhages around the smaller blood-vessels were seen in six cases. In one instance the rupture of vessels had allowed the discharge of parasites into the tissues. In most instances which we have examined the rupture of the cerebral capillaries or capillaries in other viscera has not led, as might be expected, to the discharge of parasites into the tissues. Abundant infected red cells are seen filling the vessels or tightly packed towards the vessel walls, while absence of infected red cells in the haemorrhagic zone is the rule, not the exception. In the classical work of Marchiafava and Bignami (3) these facts were fully recorded; our observations are simply confirmatory.

Pigment varying in amount was present in the lining endothelial cells, in detached phagocytes, and free in the lumen.

Nerve-cell degeneration was observed in eleven cases, as shown by cells of abnormal size and shape, loss of Nissl granules, eccentricity and distortion of nucleus to its complete disappearance. The spinal cord examined in one case showed advanced cell degeneration of the anterior cornual cells with the typical vascular changes and complete blocking of vessels. This patient had developed paraplegic symptoms before death.

*Associated lesions in the other viscera.* The possible significance of these changes will be dealt with under the corresponding organs. But in the group under consideration the local massing of parasites and lesions in these situations does not seem from a review of the clinical histories to have determined the fatal issue.

*Distribution of parasites.* Local accumulations were found most often in the spleen, marrow, heart, and pancreas; less frequently in the intestines, lungs, adrenals; occasionally in the liver, kidney, and thyroid.

Fatty and other degenerations of the cardiac muscle, acute tubal 'nephritis', vascular changes in the adrenals, terminating in tissue necrosis and all varieties of pulmonary congestion and haemorrhage, were recorded.

*Type 2, referable to embolic processes.*

Again quoting Ewing: '... the coma develops suddenly and may be as suddenly recovered from. . . . From this very transient form the duration of the coma may be much more prolonged and serious, but it is seldom fatal.' Of thirty-three cases of coma developing, often suddenly, in cases with crescents only in the blood, three were fatal. Ewing suggests that emboli of parasites, pigmented leucocytes, and phagocytes (macrophages) would explain such symptoms. In the blood are few or many crescents, sometimes subtertian parasites, very few rings or no parasites.

The comparatively low death-rate in this type of cerebral coma (three out of thirty-three) will not afford opportunity for microscopical investigation. Our results are confined entirely to fatal cases. But one case in our series is of interest in this connexion, although we do not infer that the pathology of the condition can be explained as Ewing has suggested; the history of our case is somewhat similar to Group 2 of Ewing's.

*Case XLVI.* Dvr. W. arrived in Macedonia 1915. No previous history of malaria. 23.7.17, while on 'grazing guard' fell down unconscious. On recovery next day found himself in hospital at a field ambulance. Detained for four days, discharged, and then excused duty for two days. On 30th resumed full duty, but fell down unconscious, recovering consciousness in a C.C.S. forty-eight hours later. Blood film showed subtertian rings and crescents. He became unconscious again during the day and died the same night.

*Microscopic examination.* Massing of parasites in brain, more pronounced in cerebellum than cerebrum. Thrombosis of capillaries leading to complete vascular obstruction. Fine rings and segmenting forms were present in the thrombi. Numerous parasites in spleen and pancreas. No fatty degeneration of the cardiac muscle.

In the absence of specific information to the contrary it is impossible to say whether the patient after his first attack of unconsciousness was vigorously treated with quinine. Seeing that after a four days' stay in hospital he was returned to his unit it is improbable that the diagnosis of subtertian malaria was made. Five days later sudden coma developed and was again recovered from. Such a condition as was found by the microscopic examination could hardly have been present in association with the first attack.

*Type 3*, referable to the general toxæmia of the infection.

'In these cases the coma develops slowly, but may in cachetic cases be ushered in suddenly, apparently by some embolic process. It is often of prolonged duration, and not being caused by massing of young parasites in cerebral vessels, it is unaffected by quinine. Occurring only in severe cases, and being associated with serious toxic lesions in many viscera, it is nearly always fatal.'

The parasites are usually scanty in the peripheral blood, and at the time of death are absent or scanty in the tissues.

Marchiafava and Bignami (3) pointed out many years ago that punctiform hæmorrhages were found in the brain in fatal cases of malaria without massing of parasites, ascribing the same to alterations of the endothelial lining of vessels. The actual nature of the alteration cannot be specified with certainty, but it is of interest to record that in seven cases in this series showing such punctiform hæmorrhages in connexion with the small blood-vessels, hæmorrhages of a similar nature were found in other situations.

Two cases died with hyperpyrexia (108° and 109° F.); microscopically hæmorrhages were present in the villi of the intestine and the lung alveoli. In one case there was an intradural hæmorrhage, and also hæmorrhage in the pulmonary tissue. This patient collapsed suddenly and died two hours later. In three other cases hæmorrhages were found in the intestine and lung alveoli.

The blood film examinations showed parasites to be scanty or absent,

similarly in the viscera. In the two negative cases, spleen smears and sections of the tissue gave a negative result as regards the presence of parasites, but melanin was plentiful.

The associated lesions were diffuse tubular degeneration of the kidneys and the above-mentioned haemorrhages. The adrenals were normal, and in one instance there was slight fatty change in the heart muscle.

We have records of other observations on cases of pernicious malaria which developed fits, localized or general convulsions, terminating in coma. Parasites were few or absent in sections of the brain tissue, but scattered haemorrhages extending from the congested capillaries and arterioles were prominent in the cerebral tissues.

A second series of seven cases is considered as coming under the heading of malarial coma referable to the general toxaemia. Examination of the brain, heart, adrenals, and other organs failed to demonstrate the determining cause of the cerebral or other symptoms. Here again, with one exception, parasites were scanty in the peripheral blood. This latter case had a heavy infection four days before death. No further blood examination was made. Patient died after a succession of five general convulsions.

Without entering into detail, the clinical histories of these two groups of seven cases showed points of similarity. Excluding those who died more or less suddenly (three in number), the duration of cerebral symptoms is longer than in the first type of comatose cases, varying from forty-eight hours to four or five days. Symptoms suggestive of cerebral irritation, e.g. maniacal delirium, general convulsions, hyperpyrexia, were recorded.

*Heart.* It has been the general opinion that the heart shows no important changes in malaria. Mannaberg (4) stated that 'the heart participates but little in the malarial process'. 'Apart from light grades of hypertrophy and degeneration of the myocardium with dilatation encountered in cachectics, there is no lesion positively determined to be due to malaria.' Ewing did not observe fatty changes in his cases. In one there was a notable exception to the usual rule, and very large numbers of young parasites and pigmented cells were found completely filling distended capillaries throughout the heart wall. In this case cardiac failure was the most prominent symptom. He concludes that the available evidence does not warrant a positive conclusion that acute cardiac failure in pernicious malaria may result from a massing of parasites in the cardiac muscle. Thayer (5) also notes that there are no important changes, but quotes Ewing's case just mentioned. McCrae (6) states that no changes which are characteristic are observed in the heart muscle.

Dudgeon and Clarke (1) in a previous publication pointed out that in five out of six cases of acute malaria examined microscopically, diffuse fatty degeneration of the heart muscle was present, similar in all respects to that which has been found in acute diphtheritic toxaemia. These cases occurred during the summer of 1916, when the parasites of malarial fever were acting on virgin soil, during a long period of hot weather to which our men were unaccustomed, and when

military circumstances prevented that degree of rest obtained so readily in times of peace. It is necessary to recollect these facts as at least two factors were acting in conjunction on the cardiac muscle of the malarial patients. Great attention has been paid to this question of fatty change in the heart muscle in the series of cases under review.

*Of forty-five cases of fatal malaria in whom the cardiac muscle has been examined, the result is as follows :*

Fatty degeneration of the heart muscle.	Absent . . . . . 22
Diffuse . . . . . 5	Present . . . . . 23
Moderate grade . . . . . 3	
Limited or slight . . . . 15	

*Parasites.* The capillaries were loaded with parasites in seven cases; thrombosis of the vessels was noted in two instances. In six of the seven cases the parasites were present similarly in the cerebral capillaries. The one remaining case has been included in this group as there was no other important organ involved.

It is, however, to the clinical association of acute cardiac failure with fatty degeneration of the heart muscle (Pl. 23) that we wish to draw attention, and refer to three cases in detail for this purpose.

*Case LXXI.* Dvr. J., aged 39. (Clinical notes from Capt. J. S. Fowler, R.A.M.C.) Admitted as 'D.A.H.' on 15.8.17. Cannot state whether he had had malaria previously. Reported sick twelve days before. On admission the notes state he was too ill to give a history.

On examination pallid, cachectic, slight icterus, tongue very dry and brown, crust of old herpes on lips. Temp. 100° F., pulse feeble. Lungs nil. Urine nil. Spleen enlarged. Blood film: very scanty fine rings present.

*Heart.* No enlargement of cardiac dullness. Apex beat in fifth space internal to nipple line. No bruits. 'The sounds are, however, short, muffled and toneless, reminiscent of what is heard in diphtheria. This was so marked that instructions were given that patient was to be kept absolutely flat, not even to raise his head.'

On afternoon of admission patient had a syncopal attack lasting for nearly half an hour, during which period his pulse became rapid and almost imperceptible. Next day patient had several attacks of heart failure and died at 7 p.m. He was quite conscious throughout.

*Microscopic findings:*

*Heart.* Diffuse fatty change throughout the cardiac muscle; the fat was present as fine droplets.

*Brain.* No thrombosis of vessels, parasites very scanty. No local massing of parasites in any of the viscera.

*Case XXXII.* Sgt. C., aged 35. Chronic malaria with acute exacerbation.

On examination cachectic, slight icterus, continual vomiting, quotidian fever, enlarged liver and spleen. Urine contained bile; pulse, no record of rate; the heart sounds are noted as almost inaudible.

Blood film. Very numerous fine rings, at least one red cell in three contains parasites. Three days after admission sudden syncope occurred, patient dying soon after.

*Microscopic examination.*

*Heart.* Diffuse fatty degeneration present. Marked degeneration of muscle fibres, cells swollen, transverse striation lost, while some cells were nuclear free.

Numerous sporulating parasites, both free and engulfed in the capillaries. Local accumulation of parasites seen in pancreas also. Brain: no thrombosis and no parasites seen.

In both these cases of acute cardiac failure the most important microscopical change was found in the heart muscle, that of diffuse fatty degeneration. The extent of this is well shown in the (Pl. 23), which represents the cardiac muscle of the first case reported. It is unfortunate that the adrenal was not sectioned in the light of recent work on this gland in connexion with fatal malaria; all other organs examined showed lesions of little significance.

In the third case, in which two sudden attacks of heart failure occurred in the last ten hours of life, the heart muscle showed fatty degeneration of less intense degree. Parasites were very scanty in the cerebral capillaries; no local accumulations elsewhere. The lipoids of the adrenal cortex were greatly reduced, but no degenerative changes were present. A complete microscopical examination failed to demonstrate any other striking changes.

A fourth case, dying suddenly, was associated with an acute tubal nephritis and is referred to later.

It is to be expected that in pernicious malaria, a disease with symptoms of a severe general toxæmia, the heart's action must of necessity be disturbed. Further, the obstruction of the cardiac capillaries by numerous malarial parasites, the degeneration of the muscle cells of varying degree, and fatty degeneration of different intensity (on twenty-three occasions out of a total of forty-five examinations) afford sufficient evidence that the heart muscle undergoes important changes. We have noted cases who were found dead, or who died quite suddenly, in whom fatty degeneration of the cardiac muscle was demonstrated. Syncopal attacks have been recorded in four cases showing a diffuse fatty degeneration of the muscle. The lesions in malaria being so widespread, other vital organs being profoundly affected by the general toxæmia, it is not essential that every case with fatty degeneration should during life exhibit signs of cardiac failure, although the cardiac muscle may be severely affected.

If degeneration of the cardiac muscle is found in fatal pernicious malaria, there is every reason to believe that cardio-muscular degeneration would be present in cases that recover. Every possible effort must be made, therefore, to save the heart muscle from undue exertion in this disease, a matter of some difficulty in a military campaign. It is well recognized in diphtheria that in some cases which have recovered the heart muscle was affected during the acute or convalescent stages, and we know from experience in Macedonia that cardiac complications are met with in cases convalescent from acute pernicious malaria. Fatty degeneration of the cardiac muscle, even if it is limited or slight in a microscopical section, must represent a considerable fraction of the whole muscle substance; further, in those instances in which both ventricles have been examined the fatty degeneration has been represented apparently to the same extent.

*Adrenals.* In view of the observations of Paiseau and Lemaire (7) on acute suprarenal insufficiency as a determining cause of death in pernicious malaria, the suprarenal glands have been examined in the majority of instances—in all thirty-five.

It will be well here to summarize the chief points of this syndrome to which



are attached the names of Sergent-Bernard by the French writers. The essential features are great muscular weakness, a constant low blood pressure usually less than 100 mm. Hg, no alteration of the heart's rhythm and force, pains in the lumbar and sacral regions, headache, diarrhoea and repeated vomiting, delirium and coma, and finally sudden death, which may occur with and without the previous symptoms. Acute insufficiency or hypo-epinephry is described as occurring in three clinical groups, the names of which sufficiently indicate the symptoms: (1) Pseudo-peritonitic, (2) pseudo-choleraic, (3) pseudo-meningitic.

Paisseau and Lemaire specifically state that they do not wish to convey the impression that in suprarenal insufficiency must be sought the usual cause of the pernicious access. But sometimes this clinical type can be recognized. They cite in detail three cases in which on clinical grounds this diagnosis was made. Further, in their opinion, the changes found in the adrenals on microscopical examination were sufficient to justify a diagnosis of adrenal insufficiency. It is essential to recognize, also, that no proof of loss of chromaffine in the cells of the medulla is referred to in this communication from the French authors. There is no record of a microscopical examination of the heart muscle or cerebral tissues. The absence of such important data greatly reduces the value of their clinical and pathological observations.

*Case I.*<sup>4</sup> Aged 35 years. Sudden onset of deep coma. Death three hours later. Local accumulation of subtertian parasites in spleen and adrenals, scanty in liver and kidney. Acute degeneration of glandular cells.

*Case II.* Chronic malaria and marked anaemia. Admitted in a typical algid collapse. Death about thirty hours later.

Parasites massed in spleen and suprarenals. Degeneration of cortex and haemorrhages into gland.

*Case III.* Great asthenia, lumbar and epigastric pains, vomiting and diarrhoea. Low tension pulse, choleraic facies with no loss of elasticity of skin. Patient remained in this collapsed state and died five days later.

*Adrenals.* Arterial thrombosis, haemorrhages and areas of degeneration. Massing of parasites in spleen, less numerous in suprarenals.

Returning to our results in the examination of thirty-five glands, the most constant lesion has been the reduction of the fatty lipoids of the cortical layers, usually greatly diminished below the normal, as remarked elsewhere, a change appreciable to the naked eye. In no less than thirty cases such reduction is noted, while in many instances the loss was considerable.<sup>5</sup> These changes in the adrenals occurred in cases in which the chromaffin content, as estimated by chromic acid fixation, was diminished. In many instances the pigment could not be detected.

In five cases only, other important histological changes were observed—thrombosis of capillaries with haemorrhages into the gland, degenerative changes in cortex with and without blocking of the blood-vessels.

<sup>4</sup> Résumé of the chief points of the three cases.

<sup>5</sup> Observations based on over 100 examinations of the adrenals in malaria fully confirm this statement.



The other viscera were similarly affected; e.g. cerebral capillaries were packed with malarial parasites, and in two instances the vessels were thrombosed. Local accumulations were present in other viscera, spleen, heart, and pancreas.

These five cases have already been considered under the cerebral group (type 1), in which, according to well-established views, massing of parasites in the cerebral capillaries is the pathological basis of the cerebral and other symptoms. To indicate as briefly as possible the clinical aspects of the five cases.

*Case I.* Stuporous, continued high remittent fever, anaemia, diarrhoea, no vomiting, pulse regular. Died three days later in coma.

*Case II.* Sudden collapse and unconsciousness, anaemia, pulse 92, constant hiccough. Died the same day.

*Case III.* Found unconscious. Died soon after.

*Case IV.* Admitted in deep coma, pulse 150. Died soon after.

*Case V.* Jaundice, rapid weak pulse, subnormal temperature, restless. Cardiac dilatation. Chronic interstitial nephritis. Died about thirty hours after the collapse commenced.

To attribute the fatal result in the above five cases alone to a disturbance of the functions of the adrenals would, we think, be incorrect. Probably it would be better to consider the histological changes as significant of the extensive character of the lesions in pernicious malaria. In no respects do the symptoms suggest alone a suprarenal insufficiency.

The question is of no little importance in regard to treatment, as, if there was evidence of a deficiency of adrenalin in the circulating blood, the immediate treatment of such cases might theoretically be improved by giving adrenalin. Experience has proved that adrenalin produces no permanent beneficial effects, as might be expected when it is realized that the action of this drug rapidly passes off, while severe changes in the glands are already established.

*Lungs.* It is uncommon for symptoms referable to the respiratory tract to attain any prominence in the clinical histories of pernicious malaria. In less severe clinical types of subtertian malaria the occurrence of bronchitis has been noted frequently. The older writers observed that with response of the malarial infection to quinine the respiratory symptoms have abated, a result one would expect from a study of the microscopical changes in the tissues in acute malaria. Bignami (3) has observed rusty sputum in some cases of 'bronchitis' in pernicious malaria. While it is unquestionable that true croupous pneumonia and lobular pneumonia occur as complications or sequelae in cases who at the same time are infected with the malarial parasite, no pathological evidence has been brought forward, as yet, to show that a lesion of a lung is due to the action of malarial parasites. There are, however, frequent references in the literature to atypical consolidations of lung, and the question of a 'malarial' pneumonia continually recurs without being finally answered. What exactly the 'pneumonic subcontinued' of the classical writers is must remain undecided. Mannaberg (4) states there was in such cases 'a profuse secretion of mucus, serum, and even blood into the fine bronchioles, but no deposit of a fibrinous nature'. Sometimes the sputum is

noted as bright red or intensely haemorrhagic. Microscopically, besides diplococci, red blood cells, both free and infected, have been found. Bignami observes that infected red cells rarely pass into the sputum, as the tendency so noticeable in the cerebral vessels is for them to adhere to the walls of the lung capillaries.

In this connexion a case recorded by J. H. Burgess (8) is of considerable interest.

*Case I.* Native soldier, when first seen diagnosed as pneumonia with typical symptoms of cough, pain in side, temperature 103° F. Sputum, mucoid, viscid, and uniformly blood-stained. Blood film, aestivo-autumnal parasites; differential count, polymorphonuclear 62 per cent., hyalines 14.4 per cent., small mononuclears 22.3 per cent. Total leucocyte count is not given.

During the course of the disease definite physical signs of consolidation of the left lower lobe developed. The fever showed a tertian periodicity, and a prominent feature was the alleviation of the symptoms during the afebrile periods. The sputum was still rusty eight days after the first record of its character. Three weeks later, physical signs had disappeared.

The apparent absence of a polymorphonuclear leucocytosis and the recurring remission of symptoms do at least suggest an infection of the lung of unusual character, and by an agent other than the pneumococcus.

In a recent paper dealing with the clinical types of subtertian malaria as seen in Macedonia, Falconer and Anderson (9) cite two cases of lobular consolidation of the lungs of atypical type. One case showed a disturbance of pulse-respiration ratio. No expectoration in either case. The temperature was characteristic of a malarial attack and not of pneumonia. Subtertian parasites were present in the peripheral blood. The pulse was good throughout, and at no time were the patients seriously ill. They concluded that there was no evidence of a superadded infection.

The results of our examinations of the lungs in thirty-three cases throw some light on this question of atypical consolidation of the lung in malaria.

In five instances, true lobular pneumonia with an exudate of normal character. One case of lobar pneumonia in association with pneumoconiosis (the man had been a stone-mason). These six cases can be dismissed from further consideration. The microscopical findings in the remaining twenty-seven cases were:

Marked congestion of capillary vessels of alveoli <sup>6</sup>	20	Associated lesions of 23 cases
Haemorrhages into the alveoli	12	
Haemorrhages into the alveoli and the connective tissues	3	
Haemorrhages with inflammatory foci additional	5	
Oedema, hypostatic congestion, or partial collapse	12	
Absence of either marked congestion or alveolar haemorrhages	4	

No record is available as to the characters of sputum, if any, in the twenty-

<sup>6</sup> Areas of collapse are often associated with the vascular phenomena and occur in the regions of most intense engorgement.

three cases which showed microscopic changes in the lungs, apart from the fact that the expectoration is stated to have been watery on a few occasions. In four only is mention made of symptoms or signs indicative of bronchitis or pulmonary lesions. This is to be expected, as the gravity of the cerebral symptoms or phenomena of collapse dominate the clinical picture; many were too ill to give a history, or were moribund when first seen.

The congestion of the smallest blood-vessels of the lungs is in keeping with the familiar congestion of the other viscera. It is this engorgement that responds to quinine, just as the congestion of the spleen declines under satisfactory anti-malarial treatment and for a similar reason.

The occurrence of haemorrhages into the lung alveoli does not seem to have attracted much notice in the accounts of the morbid anatomy of pernicious malaria. Usually quite limited in character, most often confined to the lower lobe or posterior portions of the lungs, they have suggested from their appearance small areas of collapse, hypostatic congestion, broncho-pneumonia, but never infarction. Only exceptionally has it seemed possible that from the extent of the haemorrhages the physical signs of consolidation could be recognized during life. We have records of two cases which were diagnosed clinically as broncho-pneumonia, although the features of the disease were somewhat masked by the severe malarial infection. The diagnosis of broncho-pneumonia was made at the post-mortem examination, but the microscopical investigation of the affected tissues was not confirmatory. The microscopical findings were as follows: Haemorrhage into the lumina of the bronchi, considerable dilatation of the capillaries in the alveolar walls, diapedesis of red cells, and foci of alveoli filled with red blood-cells. There was complete absence of cellular reaction, but detached mononuclear cells filled with golden brown pigment were conspicuous. Phagocytosis of red cells occurred, but was not a marked feature. Patches of oedema and collapse were in close proximity to the haemorrhagic areas.

There is no doubt that the cause of pulmonary haemorrhages is to be sought in the congestion of the alveolar walls and accompanying tissue changes. We regard the congestion and haemorrhages in the pulmonary tissues as similar to the congestion and haemorrhages met with in the brain, and to a much more intense degree in the spleen. In fact, congestion of the blood-vessels and haemorrhage into the surrounding tissues is one of the most striking phenomena met with in acute pernicious malaria.

The following cases are worthy of record in relation to pulmonary consolidation:

*Case I.* Gnr. M., aged 18. Chronic malaria with recurrences. Clinical pneumonia.

Previous history. Two years in Macedonia, and four previous attacks of malaria. Present illness commenced with headache, general pains, shivering. Temp. 101.4° F.

On admission to C.C.S. temp. 105.2°. Dull, drowsy, tongue thickly furred, rapid pulse, spleen enlarged.

The following day the patient was worse, and moist sounds were heard

all over the chest, while twenty-four hours later consolidation was diagnosed at the right base. Patient rapidly became worse and died on the eleventh day of his illness. Blood films were negative at each examination. Smears of the splenic juice showed coarse pigment, but no malarial parasites. Both lungs were found to be oedematous and congested, very dark in colour, with patchy consolidation. Spleen was very much enlarged.

*Microscopy of the tissues.* *Brain.* No thrombosis, no parasites, and no haemorrhages.

*Kidney.* Diffuse degeneration of the tubular epithelium, more especially of the convoluted tubules.

*Lungs.* Considerable congestion of the alveolar walls with haemorrhages into the lung tissue producing a patchy consolidation (Fig. 4). In some areas the haemorrhages occupied a large area of lung tissue as in a true apoplexy. There were scattered areas of oedema and very early inflammatory changes, which in the case of the left lung were insufficient to produce consolidation, while in the opposite lung very small foci of consolidation due to active inflammation were present in direct relation to the haemorrhagic areas. Active red celled phagocytosis was present in each lung.

*Case II.* Subtertian malaria. Haemorrhages into lungs and intestines, skin, and gums.

*Previous history.* Four to five months in Macedonia with no history of malaria. Present illness commenced on 8.10.17 with general pains, weakness, and anorexia. On examination tongue furred, bleeding from the margins of the gums, numerous scattered petechiae over trunk, scanty over limbs. Temp. 105° F. 9.10.17, subtertian rings, sporulating forms. Total red cells, 4,500,000 per c.mm. Leucocytes, 3,400 per c.mm. 10.10.17, severe epistaxis, vomited large quantities of dark blood; collapsed and died early next day.

*Post-mortem.* *Lungs.* Numerous small dark-red patches, about  $\frac{1}{4}$  in. in diameter, in both lungs.

*Stomach.* Intense congestion, submucous haemorrhages, limited abruptly by pylorus. Large haemorrhage in stomach.

The intestine in its upper part contained altered blood but no submucous haemorrhages. No other important findings. Spleen soft, slightly enlarged.

*Microscopic examination.* *Stomach.* Extreme congestion of surface mucosa. Haemorrhages into the tissues. Parasites very scanty. Melanin, intra- and extra-cellular, very abundant.

*Brain.* No thrombosis.

*Heart.* No fatty change.

*Lung.* The alveolar capillaries are very congested; extensive haemorrhages seen over a large area of the lung and into the lumina of the bronchi. No acute inflammatory changes.

*Pancreas, liver, and kidney.* No important changes.

This case is really an example of a haemorrhagic type of pernicious malaria, haemorrhages having taken place in many other situations besides the lungs.

Further observations are necessary to determine the clinical significance of these alveolar haemorrhages in malaria. Records of the chemical and microscopical examinations of the sputum, where present, and total and differential blood-counts in cases with signs of bronchitis or atypical consolidation would be of great value. Our observations show that in pernicious malaria scattered areas of consolidation of the lung tissues occur in which the anatomical basis is diapedesis of red blood-cells into the alveolar spaces, in extent usually of limited character, but in exceptional cases producing massive consolidation of lung tissue.

The extent of the palmonary congestion or haemorrhages is not related to a heavy injection at the time of the termination of the disease.

*Kidney.* In subtertian malaria an albuminuria, slight in amount, is usual (58.3 per cent. of 165 cases, Thayer) (5). Further, in fatal cases, degenerative lesions especially affecting the epithelium of the convoluted tubules are common. The relation of malaria to nephritis is not so vexed a question as that of malaria and pneumonia. Thayer considers it not an uncommon sequel (1.7 per cent. of 1,832 cases). In subtertian malaria it is by no means infrequent; its course is that of a toxic nephritis. Of Thayer's twenty-six cases, fourteen recovered, four died, six fate unknown, two developed chronic nephritis.

Summary of kidney changes (our cases). Of forty-six examined, forty-two showed diffuse tubal degeneration, four showed no degeneration or swelling of the epithelium of the convoluted tubules, but autolysis was present.

*Parasites.* In three cases the renal capillaries contained very numerous infected red cells; the cerebral capillaries also showed a similar condition.

Extensive fatty degeneration was found in one case, while scattered fat was recorded on ten occasions out of a total of twenty-four specimens examined for this purpose. Free iron granules were not found, except as a very scattered deposit.

Oedema and exudation into Bowman's capsule was noted; congestion of the tufts was frequently met with, also haemorrhages and sometimes patchy necrosis. The epithelium of the tubules, especially the convoluted, showed extensive degeneration; the tubules contained degeneration products on numerous occasions.

Pigment was seen in many situations—in the glomeruli, in the endothelial cells of the blood-vessels, in the connective tissue cells between the tubules, in the cells lining the straight tubules, and free in the lumina. Yellow brown granules were also seen in the epithelium of the straight tubules.

Changes in the red cells occurred, polychromatophilia, partial and complete haemolysis, and agglutination.

There are two cases in this series where the symptoms referable to the kidney dominated the clinical picture.

*Case I.* Pte. M., aged ? Malaria in April 1917. No previous history of other illness.

22.11.17. Swelling of legs and feet, dyspnoea, vomiting, cough and hoarseness. Râles over both lungs. Urine, albumin present.

26.11.17. At C.C.S. slight oedema of eyelids, feet, and hands. Blood film: crescents, no rings. Urine: no albumen. Death the same day after five 'uraemic' fits.

No important observations at post-mortem beyond hypostatic congestion of lungs and a very enlarged spleen.

*Microscopical examination.* *Brain.* No thrombosis. Pigment plentiful in liver, spleen, pancreas, and lung.

*Kidney.* Acute tubal nephritis with extreme tubal degeneration. No evidence of chronic nephritis.

*Lung.* Great congestion of alveolar vessels, haemorrhages into the alveoli, endothelial cell proliferation, and phagocytosis of red cells.

The duration of illness as judged by the history is five days or a little more.



An important negative finding is the absence of cerebral accumulation of parasites. There is no evidence of acute malaria, and the probable explanation is that the nephritis is the sequel of malaria.

*Case II.* Dyr. B. Chronic malaria. On examination oedema of face and legs of two days' duration, dyspnoea, cough, general weakness. Had just left hospital after malaria. Blood film: a few rings and numerous crescents. Urine: albumin present, blood, and epithelial casts. Palpable spleen, dullness at both bases. Temperature, 99° to 100° F. Pulse, 54 to 68. He improved for four days, then during conversation with his Medical Officer breathing suddenly became stertorous, rapidly assuming the Cheyne-Stokes type, pulseless and sweating. Died two minutes later.

*Kidney.* Acute diffuse tubal nephritis.

*Heart.* Diffuse fatty change.

The connexion between malaria and the kidney lesion is fairly clear. The man was admitted with a relapse of subtertian malaria and acute changes were present in the kidneys; he succumbed owing to the diffuse fatty degeneration of the cardiac muscle. In the absence of further details as to site of local accumulations of parasites, this case cannot be considered so typical an example of the direct relation of malaria to kidney changes as Ewing's case of acute haemorrhagic nephritis in malaria. The massing of parasites in the kidney had produced thrombosis of vessels with numerous miliary haemorrhages, thus bringing the kidney into line with the pathogenesis of the other two well-known groups, the cerebral and gastro-intestinal.

*Intestine.* Symptoms referable to the intestine in malaria are frequent, but only rarely do they assume a severe character. In the common mild variety the usual complaint is of diarrhoea with or without admixture of blood. In a country where dysentery and malaria are rife, it is to be expected that both infections may be present at one time. Graham (10), in examining stools in all cases of malaria passing blood or blood and mucus, isolated dysentery bacilli in sixty-two out of sixty-six cases; repeated bacteriological examination was not possible in the four negative cases. But there are also cases of malaria whose symptoms at most are a bloody diarrhoea, whose stools microscopically and culturally are not those of bacillary dysentery, and in whom the origin of the blood is due to the action of the malarial parasite. Graham mentions two such cases. Logan (11) studied bacteriologically samples of blood and mucus from forty-four cases of proved malaria. He found *Entamoeba histolytica* on three occasions, and together with *B. Shiga* once, *B. Shiga* alone in nineteen cases, *B. Flexner* Y in nine, and 'in-agglutinable dysentery bacilli' in five. In the seven negative cases dysentery bacilli were isolated, on the second or third attempt in five.

The microscopic changes found in fatal cases of malaria are in support of the clinical observations. The intestines from eleven cases were examined, and the most constant finding was a congestion of the blood-vessels, and less frequently haemorrhages into the villi and submucosa. In three instances in which the cerebral capillaries as well as those of other viscera were obstructed by infected red cells, the intestinal capillaries were in a similar condition. Small haemorrhages into the tissues of the submucosa and villi, localized patches of necrosis without actual ulceration or inflammatory foci, were noted. In one the necrotic



patches of mucosa had separated. In another case referred to elsewhere with haemorrhages into several tissues, the vessels in the mucosa of the stomach were intensely congested and numerous submucosal haemorrhages were present.<sup>7</sup>

*Pancreas.* The most definite changes in the histology of the pancreas occurred in those cases in which massing of parasites in the blood-vessels was observed. The outline of the capillaries, which were congested in some areas and packed with infected red cells, afforded a striking picture. Deposits of melanin were commonly observed, both intra- and extracellular. The islets of Langerhans in a few cases showed degenerative changes. Haemorrhages into the pancreatic tissue were noted on several occasions in association with haemorrhages in other organs. No symptoms referable to the pancreas were recorded, but traces of sugar in the urine were an occasional finding.

*Spleen.* The histological changes met with in the spleen in malaria are too well known to require further description, except for a few points of special importance. Congestion and oedema were the usual microscopical findings, but haemorrhages, often of wide extent, were of common occurrence. The changes in the Malpighian corpuscles are inconstant. In some cases these bodies were reduced in size, while in others they were extremely prominent. Endothelial cell proliferation in the central areas of these bodies was not infrequent, while in some cases these endothelial cells had undergone partial or complete necrosis.<sup>8</sup> Melanin deposits were the rule. This pigment, often in considerable amount, was found both free and intracellular, phagocytosed by endothelial cells and small giant cells, and in the intima of the blood-vessels. The phagocytosed pigment was present as dots, clumps, and apparent rod-shaped bodies. Phagocytosis of red cells by the lining endothelial cells or similar cells detached may give a striking picture in sections of the spleen. Parasites were frequently met with in enormous numbers, but it has been long recognized that smears of the spleen may afford valuable information in this disease. In one case in which an area of splenic tissue had undergone complete necrosis from the vascular obstruction, no parasites were seen in the necrosed area, but in the adjoining vascular and haemorrhagic area 'dots' and rings were present in enormous numbers. There was a continuous but low degree of pyrexia. It would suggest that the parasites present in the congested area before the necrosis occurred had undergone lysis when the destruction of the tissues took place, or a heavy infection of the blood occurred subsequent to the necrosis.

*Liver.* The changes in this organ are numerous. On six occasions, out of a total of fifty-one cases examined, the central areas of the liver had undergone necrosis; fatty degeneration was recorded in fifteen instances. The free iron reaction, already referred to under the kidney section, is absent or very slight in

<sup>7</sup> The work of Lieut.-Col. Graham and Captain Logan is especially valuable as serving to prove the necessity for bacteriological examination of the faeces of malaria cases who are passing blood and mucus. The 'diagnosis' of haemorrhage due to malaria without satisfactory bacteriological investigation is to be deprecated.

acute pernicious malaria, a finding in direct contrast to the results which we have obtained in chronic anaemic malaria. Haemorrhages were infrequent; collections of mononuclear cells in the portal areas were of rare occurrence. Melanin was found as typical black pigment in the sinuses, free and engulfed by the phagocytic mononuclear cells of the hepatic sinuses. No histological changes worthy of a special reference were noted in the thyroid, bone-marrow, testicles, and pituitary body.

The iris and retina have been sectioned in several cases of pernicious malaria. Definite obstruction of the capillaries was observed; in other instances no true obstruction was present, but the red cells infected with parasites showed the common tendency to drift to the wall of the vessel.

*Examination for spirochaetae.* Sections of various organs from cases of pernicious malaria, more especially from fulminating cases and from patients dying from this disease in whom no parasites were found in the blood films, were examined for spirochaetae, but with negative results in every instance.

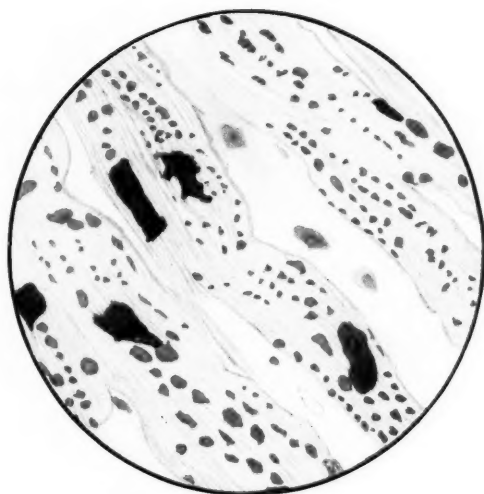
*Melanin.* We have already drawn attention to the fact that the free iron reaction in the tissues in acute malaria is insignificant, while in chronic malaria, associated with anaemia, an intense reaction may be demonstrated. This reaction is as marked in the liver, spleen, and kidneys as that with which we are acquainted in pernicious anaemia. By so-called 'unmasking methods', to which reference will be made in detail in a later report on Blackwater Fever, it is possible to demonstrate the iron reaction in malaria in tissues which fail to respond to the usual tests. Ewing (2) considers that there are four classes of pigment in the tissues in malaria: (1) melanin; (2) an iron pigment found chiefly in the cells of the liver, spleen, kidney, and bone-marrow; (3) haematoidin, which occurs as granules or crystals of dark-brown colour; (4) Urobilin or bilirubin, seen in cases of jaundice and deposited as granules or crystals.

*Examination of the tissues for an intracellular parasite.* During the epidemic of pernicious malaria in 1918, certain tissues were especially examined for the presence of an intracellular form of the malarial parasite, but so far without success.

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## REFERENCES.

1. Dudgeon and Clarke, *Lancet*, Lond., 1917, ii. 153.
2. Ewing, *Journ. of Exp. Med.*, New York, 1901-5, vi. 119.
3. Marchiafava and Bignami, *The Parasites of Malarial Fever* (The New Sydenham Society), 1894, cl.
4. Mannaberg, 'Malaria', *Nothnagel's System of Medicine*, 1899, ii.
5. Thayer, 'Malaria', *Allbutt's System of Medicine*, Lond., 1907, ii. 241.
6. McCrae, 'Malaria', *Osler and McCrae's System of Medicine*, Lond., 1909.
7. Paiseau and Lemaire, *Bull. Acad. de Méd. de Paris*, 1916, lxxvi. 300.
8. Burgess, J. H., *Indian Medical Gazette*, Calcutta, 1907, xlii. 131.
9. Falconer and Anderson, *Lancet*, Lond., 1907, xlii. 131; 1917, i. 607.
10. Graham, *ibid.*, Lond., 1918, i. 51.
11. Logan, Report by Capt. W. R. Logan on 'Malarial Dysentery' to D.M.S., British Salonika Force, 1916.



Section of Cardiac Muscle. Stained with Scharlach R. and  
Hæmalum.  
Case of Pernicious Malaria, showing extreme degree of Fatty  
Degeneration of Cardiac Muscle.



# OBSERVATIONS ON THE CLINICAL APPEARANCES OF BILHARZIASIS IN AUSTRALIAN TROOPS, AND THE SIGNIFICANCE OF THE SYMPTOMS NOTED

By N. HAMILTON FAIRLEY

THIS paper is based upon a careful analysis of seventy-five cases of bilharziasis occurring amongst troopers of the Australian Light Horse in Egypt. In 1916 these men were stationed, for the most part, in the Sweetwater Canal zone, especially at Serapeum and at Tel-el-Kebir.

Amongst the fellaheen of Egypt multiple infections with different diseases so commonly exist that it is often a matter of considerable difficulty to correlate the clinical picture with the various aetiological factors concerned. This is not the case with white troops, and for this reason it is of importance to record accurately the early clinical and laboratory observations on uncomplicated cases of bilharziasis.

Clinically bilharziasis, at least as it has manifested itself amongst Australian troops, can be divided into two stages:

(a) An early stage which is frequently observed occurring four to ten weeks after infection; hereafter I shall refer to this as the toxæmic<sup>1</sup> stage of disease.

(b) A much later stage of localized disease, characterized on the one hand by vesical symptoms in *B. haematobia* and by intestinal symptoms in *B. mansoni* infections on the other. Symptoms of this stage may appear from three months up to two and a half years after infection.

## Stage A. Initial Toxic Symptoms.

The initial toxic symptoms associated with bilharziasis were first described in *Bilharzia japonica* infection by Japanese observers. Excellent descriptions have been given by Edgar (1), Bassett-Smith (2), Miyagawa (3), and Laning (3a). These symptoms are known in Japan as 'Katayama Disease'.

In *B. mansoni*, Flu (4), in 1911 in the West Indies, called attention to

<sup>1</sup> No apology is necessary for insisting on the essentially toxic basis of these early obscure clinical symptoms in bilharziasis. Elsewhere (*Journ. R.A.M.C.*, April, 1919; *Lancet*, June 14, 1919, pp. 1017-20) I have adduced evidence to prove the existence of a toxin circulating in the blood, the product of maturing or of adult worms. Thus: (1) Monkeys hyperinfected with bilharzia cercariae (especially *B. haematobia*) die within two to four weeks of exposure and before ova have been deposited in the tissues. (2) In man, as in experimentally infected monkeys, the presence of an immune body can be demonstrated by means of a specific complement-fixation test; the antigen being prepared from cercariae contained in the livers of the intermediary hosts, *Bullinus dybowskii* and *Planorbis boissyi*. (3) The existence of an eosinophilia in the blood and of an increase in the eosinophil myelocytes in the bone-marrow suggests a circulating toxin exerting some chemiotactic influence on the tissues.



febrile symptoms in this infection resembling the foregoing. Archibald, in the Soudan in 1914, suggested that pyrexia in intestinal bilharziasis was due to associated secondary infections. In 1916 Lawton (5) described an outbreak of bilharziasis amongst Australian troops in Egypt, in which the initial symptoms tallied almost with those detailed by Laning for the Japanese disease.

In *B. haematobia* infection, on the other hand, none other than localized or vesical symptoms had ever been described.

In the present paper, in addition to confirming and extending Lawton's observations on *B. mansoni*, I wish to record the occurrence of a definite toxæmia in single *B. haematobia* infections.

Thus in all known forms of bilharziasis in man early toxæmic symptoms may occur. Laning would classify the symptoms of Japanese bilharziasis, according to the time incidence, into three stages.

(a) An initial stage with a high afternoon temperature lasting three to five weeks, with oedema, urticaria, pains in the upper part of the abdomen, paroxysmal cough, perhaps associated with pulmonary dullness, bowel disturbances, and high eosinophilia.

(b) A second stage, characterized by emaciation and loss of weight, the passage of mucus and blood in the stools, associated with ova and perhaps tenesmus; enlargement of the liver and spleen occurs with a marked eosinophilia.

(c) The third or terminal stage may, or may not, supervene three to five years after infection, especially in hyper-parasitized individuals. The liver is cirrhotic, sometimes enlarged, sometimes shrunken; there is ascites, oedema of extremities, marked anaemia, and dysenteric symptoms. The patient may die from exhaustion or of some terminal infection.

Lawton (5) in 1916 described the symptoms of the early stages of *B. mansoni* as follows: abdominal pain, enlargement and tenderness of the liver and spleen, pyrexia, bronchitis, a blotchy urticaria, and diarrhoea associated with blood and mucus and the passage of lateral-spined ova. Eosinophilia was high, 50 per cent. in three cases. The onset was often insidious and the incubation period varied from four to eight weeks. The pyrexia lasted from ten to fifty-six days; emaciation was a marked feature. He considered that all the symptoms were expressions of a pure *B. mansoni* infection, but subsequent investigations, both in Australia and Egypt, have shown that they were really cases of double infection.

*A description of initial Toxic Symptoms observed in a group of B. haematobia Infections.*

In the middle of July 1916 seven soldiers bathed in a pool at Serapeum<sup>2</sup> on the Freshwater Canal. Early in September—that is to say, within six weeks—

<sup>2</sup> A number of troopers were infected in the Sweetwater Canal at Serapeum. Careful examination of both the urine and faeces of these cases showed only terminal-spined ova (*B. haematobia*). Subsequently Major P. H. Bahr D.S.O., R.A.M.C., and the writer repeatedly inspected the Sweetwater Canal zone. Though *Bullinus* snails (the molluscan intermediary of *B. haematobia*) were present in large numbers, those of the *Planorbis* genus were extremely rare.

five of them were admitted to hospital suffering from an acute febrile disease; it was characterized by pyrexia, rigors, frequent sweats, headache, and generalized body pains. In a period of from four to ten days after admission urticaria supervened. In such a typical case the swelling started in the orbital region, causing such a puffiness of the face that the patient could only peep out of the swollen lids with difficulty; soon a similar oedema of the trunk, limbs, penis, and scrotum supervened.

The size of each individual wheal varied from a small isolated patch, of the size of a sixpenny piece, to the involvement of large areas, as, for instance, that of the whole hand. These elevated swellings were white in colour and tended to pit on pressure and caused intense pruritus.

This rash lasted a variable time, but disappeared as abruptly as it commenced. In some of the cases it persisted for as long as seven days. Emaciation was a feature of the illness, the duration of which lasted from ten days up to five weeks. Subsequently, however, all signs of the disease disappeared and the patients returned to duty. During the next three months all these five cases developed symptoms of localized vesical bilharziasis, such as scalding on micturition and a terminal haematuria; terminal-spined ova were found in the urine of all five and also in the faeces of three of them. A leucocytosis of 10,000 per cm. with an eosinophilia of 9 per cent. was the average count of the remaining two out of the seven, neither of whom suffered from an initial toxæmia; one has recently been admitted to hospital with vesical bilharziasis, while the other, though slightly troubled with suprapubic irritability, has not yet had to leave his regiment.

In this group of cases, as indeed in all those with these initial toxic symptoms, after a period of convalescence, the patient regains practically normal health and weight.

Nothing more is noted until the stage of localized disease is reached; this may supervene at a period of from three to twenty-four months after exposure to infection.

The histories of the remaining eighteen cases differed in no salient particulars from those described by Lawton; their classification being based on histories obtained from the patients themselves several months after infection, and not from my own personal observation during the pyrexial period, they will not be further discussed.

An analysis of seventy-five cases of bilharziasis of either species or of double infections with both parasites (*B. haematobia* or *B. mansoni*) shows that thirty-eight, or 50.8 per cent., presented early toxic symptoms. They have been classified according to the symptom-complex in the following manner:

On the other hand, at Tel-el-Kebir (Rifle Range Canal) troopers were frequently found to have terminal-spined ova in their urine and lateral-spined ova in the faeces. Investigation of this locality showed the presence of infected *Planorbis boissyi* and *Bullinus dybowskii*, and monkeys were infected with cercariae derived from these snails and the adult worms ultimately recovered from them. In this manner a remarkably instructive confirmation of Leiper's original work was established.

- (1) Cases presenting symptoms of urticaria and prolonged pyrexia.
- (2) Cases presenting symptoms of urticaria and pyrexia of less than ten days' duration.
- (3) Cases with urticaria alone.

Of twenty-three cases classified in group (1) thirteen were mixed infections, seven were cases of single *B. haematobia*, while three were definite *B. mansoni* in whom an associated vesical infection could not be excluded. It is unnecessary to dwell any longer upon the initial pyrexia with its associated phenomena, as these have already been described above.

In group (2) there were ten cases with a clinical picture such as this: A transient febricula with anorexia and a general feeling of malaise. The initial intestinal disturbance was manifested by nausea and vomiting and occasionally diarrhoea without blood and mucus; together with this there was headache and body pains. In some cases there was cough, and in all abdominal uneasiness or actual hepatic pain. The onset usually occurred four to ten weeks after exposure to infection. In taking histories of bilharzia patients I obtained the following story which is worthy of record. In July 1916 sixteen men swam in the Rifle Range Canal at Tel-el-Kebir; subsequently, six to eight weeks afterwards, ten developed symptoms of some description, although I was unable to interview all of them. The characteristic swelling of the cheeks and face became popularly known as 'the Duffus swelling', after the man who first presented this peculiar appearance. The urticaria disappeared during the day, frequently to reappear again at night-time. Pruritus was marked, and frequently the trunk and limbs were involved.

Five could not be followed up for various reasons; seven were admitted to hospital with symptoms of bilharziasis, four for other disease, in three of whom terminal-spined ova were found associated with an eosinophilia.

In group (3) there were five cases with a history of an apyrexial urticaria supervening four to ten weeks after exposure to infection. The rash consisted of white, itchy, elevated urticarial patches confined to the neck and limbs and only rarely involving the face.

*An explanation of the pathological basis of these symptoms.* As none of these cases were fatal this could not be obtained from man. Resort was had to an experimental study of heavily infected monkeys. In these animals ten weeks after infection with *B. mansoni* a curious condition was found post mortem. The chief features were an acutely congested liver with disseminated whitish tubercles, 1 mm. in diameter, on the surface and scattered throughout the substance. The spleen was definitely enlarged and congested. The colon showed pericolicitis with adhesions, subperitoneal nodules, congestion of the mucosa, with submucous infiltrations composed mainly of eosinophil cells.

The adult worms themselves were found in the superior and inferior mesenteric veins and in the portal radicles of the liver. Macroscopic lesions of the bladder and lung were quite exceptional, though ova were found to be widely disseminated by digesting the tissues with caustic soda.

In *B. haematobia* infections similar macroscopic lesions were produced, except that the pelvic organs, such as the bladder and uterus, showed vesical papillomata and greyish nodules scattered throughout the latter. In the lung there were similar accumulations resembling closely that of a miliary tuberculosis.

The adult worms, although plentiful in the mesenteric and portal veins, predominated in the pelvic plexuses, as the vesical and the uterine.

They also migrated via the inferior cava to the pulmonary capillaries, where they could be demonstrated.

Microscopically, in both infections the organs showed congestion of the vessels and cloudy swelling of the parenchyma cells. This was especially marked in monkeys dying within four weeks of infection. Typically the liver showed periportal infiltration with eosinophil and round cells, and in such situations as ova were deposited there were plasmodial aggregations of giant cells. Central degeneration in the liver and lung actually led to the formation of small abscesses composed mainly of eosinophil cells. The healing of these foci appears to be by granulation tissue and fibrosis.

There is no need to describe these lesions in more detail, but one should note that their distribution in any given organ is dependent upon the blood-supply; thus in the liver it is in the periportal zone; in the lung, in the region of the pulmonary arterioles; in the hollow viscera, such as the colon and bladder, they are subperitoneal and submucous.

The latter circumstance explains perhaps the clinical resemblance between bilharzial and amoebic dysentery, for in both these infections the principal lesion is in the deeper layers of the intestinal tube; whereas in the acute bacillary disease the initial lesion involves the mucous surface only from without inwards. The correlation between the pathology and the clinical appearances of these early infections is thus complete and the pathological basis is established. Thus one can now explain the enlargement and tenderness of the liver in both *mansoni* and *haematobia* infections and the pulmonary symptoms—bronchitis and broncho-pneumonia—especially in the latter.

An eosinophil leucocytosis accompanied by an excessive eosinophil production in the bone-marrow is constantly present in monkeys recovering from the acute disease, and positive complement-fixation reactions appear invariably in these animals sooner or later.

I would once more emphasize that the toxæmic shape is common to infections with both worms; but now it is proposed to deal with the symptoms of localized bilharziasis, which differ in several essential points in both species.

#### *Stage B. Symptoms of Localized Bilharziasis.*

##### *(1) Clinical Picture of Vesical Bilharziasis (B. haematobia).*

Forty-five cases of vesical bilharziasis resulting from a pure infection with *B. haematobia* afford the basis for this description.

The incubation period of the disease varies, according to the presence or

absence of toxæmic symptoms and the time at which symptoms of localized bilharziasis are first noted. If the initial stage is present, as occurred in 50.6 per cent. of the series, then the incubation period is to be reckoned as one of from four to ten weeks, that is from the time of exposure to infection up to the first appearance of toxæmia. On the other hand, should this initial stage be absent, as occurred in 49.4 per cent. of the series, then the onset of the localized symptoms must be regarded as the incubation period, and this is a very variable one—that is, from three months to two and a half years.

Cases such as these are a special danger to the community, for they continue to pass the ova in their dejecta, although in perfect health. These may be termed cases of latent bilharziasis, of which I have amassed records of ten.

*Mode of onset.* In 60 per cent. of cases the earliest symptom was a burning urethral pain on micturition, and after this had persisted from one to four weeks a terminal hæmaturia was noted. In the remaining 40 per cent. the pain was deep-seated or perineal, associated with an aching in the loins, frequency of micturition, and terminal hæmaturia.

*Hæmaturia.* The most characteristic of all symptoms of vesical bilharziasis is a *terminal hæmaturia*: this arises from friable granulation tissue, or, it may be, ulceration of the bladder wall, and later from the characteristic polypi themselves.

The factor originating actual hæmorrhage from this granulation tissue, which does not occur when the viscus is distended, is possibly accounted for by the muscular contractions of the bladder at the end of micturition.

In the same way the appearance of ova, which are present in greatest numbers in the last few cubic centimetres of residual urine, may be explained.

This terminal hæmaturia may occur with every act of micturition, or it may not. There are cases who pass blood but once a day, or at an interval of several days, for weeks or even for months; its occurrence is to be explained by the extent, nature, and situation of the vesical lesions.

The blood itself is usually bright red in colour; rarely it may be dark, and occasionally long worm-like blood-clots have been noted. Violent exercise, especially horse-riding, aggravates the hæmaturia, whilst rest and dietetic and palliative treatment in hospital may cause it to disappear, temporarily at any rate.

*Pain.* As a rule pain is by no means a dominating clinical feature.

*Perineal pain*, when present, is nearly always deep-seated.

*Urethral pain* may take the form of scalding on micturition. Pain referred to the end of the penis is quite common and may often be elicited by suprapubic pressure.

*Suprapubic pain* is by far the commonest type, especially when the bladder is distended; it is generally described as a dull ache which is aggravated by any increase in abdominal tension, such as is produced by tightening the belt, or by manual pressure during abdominal palpation. It is instantly relieved when the bladder is emptied.

*Backache* and pain referred to the *iliac fossae* is also common. This is most



probably a pain referred from the bladder, since, in the early stages of the disease at any rate, it is hardly likely to be due to any renal complication.

*Frequency of micturition.* Frequency is usually an early and transient symptom which lasts some four or five weeks and may be nocturnal in character. Those cases in which it was intractable were found to have some secondary urinary infection such as *B. coli* bacilluria: especially was this the case when complicated by gonorrhoea.

*Urgency* is a common complaint, so much so that some patients were unable to contain their water unless this desire was immediately complied with, and in one such case the first symptom of the disease noted was the passage of a few drops of blood-stained urine. Prof. Madden (6) informs me that he has seen cases in whom the first warning of bilharziasis was the nocturnal emission of blood-stained semen.

*Rectal symptoms in vesical bilharziasis.* It is quite common, much more so than has hitherto been supposed, to elicit a history of the passage *per rectum* of blood and mucus, though the patient himself may not regard this symptom as a true dysenteric attack. In these cases, the terminal-spined ova are present in the faeces, as well as in the urine.

Digital examination of the rectum itself revealed a tender spot just above the prostatic lobes, between the vesiculae seminalis. Rectal polypi were never found in this series. A definite enlargement of the prostate itself has not been noted at this early stage of the disease, though Madden has recorded it as occurring in heavily infected Egyptians with initial vesical symptoms.

*Cystoscopy.* The earliest cystoscopic examination was made fourteen days after the appearance of symptoms, or within five months of primary infection. In this case the blood-vessels of the trigone were dilated, and elevated sub-mucous nodules, of a glistening white colour, were visible in the urethral triangle.

In the later and more chronic stages of urinary bilharziasis Madden has described the cystoscopic appearances of the infiltrated mucous membrane as resembling wet sea-sand, patches of which are especially prone to occur in the trigone, or, again, groups of papules or even yellow ulcerations with congestion of capillary vessels may project from the mucous membrane. On these 'sandy patches' papillomata may occur in the trigone and around the ureteric orifices. Vesical calculi may be present, and, owing to the large number of calcified ova, the light reflex is altered from a white to a bright yellow colour, which gives the infiltrated nodules a very characteristic sparkling appearance.

*The urine.* On standing, the urine generally shows a deposit of mucus, phosphates, and red blood-cells.

In long-standing cases, secondarily infected with pyogenic organisms, a most copious precipitate of pus may be present.

*The specific gravity* is generally about 1,020; the reaction acid to litmus and albumin may be present in small quantity. On centrifuging bilharzia urine, pus cells and red cells are generally found in the residuum: these may be present without visible terminal-spined ova.



I have several times noted nothing but pus cells in the urine of well-known bilharzia cases, in whom numbers of terminal-spined ova could be demonstrated at a subsequent date; so sporadic is their appearance, that it is by no means advisable to exclude a diagnosis of urinary bilharziasis as the result of a single laboratory examination. The pathologist should insist upon repeated examinations of any suspicious case.

The quest for ova is materially assisted by attention to details in the collection of specimens for laboratory examination. The last few drops of urine passed give the most satisfactory results. A microscopic examination of the centrifuged deposit must be made with a low power, and is rendered still more accurate by the employment of the dark ground of illumination.

An important point which may assist laboratory workers to distinguish between a bilharzial ulceration, in which the passage of ova is either sporadic or scanty, and lesions of septic or renal origin, is the fact that the majority of the pus cells in the bilharzial exudate are eosinophils, which can be demonstrated by appropriate staining methods.

*Faeces.* Terminal-spined ova were eventually found in the excreta of fourteen cases, after a careful search, and it is probable that, with care, such ova can be demonstrated in the majority of pure *B. haematobia* infections. Contrary to expectation, the most favourable stool for this purpose is one of solid consistency with patches of thick yellow or blood-stained adherent mucus, and it is in a small portion of this, when teased out in saline, that the characteristic ova will be found.

*Blood.* Investigation of the leucocyte variation in vesical bilharziasis. In the stage of localized bilharziasis the blood-picture differs considerably from that of the initial toxæmia. At this, the more chronic period, the total leucocyte count, as well as the percentage of eosinophils, has decreased.

In a series of thirty-four cases the average count was 10,030 per c.mm.; the lowest, 4,700; the highest, 21,870.

In thirty-six cases the average differential count was as follows:

Polymorphonuclears . . . . .	45.1 per cent.
Lymphocytes . . . . .	28.2 „
Large mononuclears . . . . .	12.6 „
Eosinophils . . . . .	13.5 „
Basophils . . . . .	0.6 „

In a series of forty-six cases in which especial attention to the eosinophilia was paid—

In 7 it was under	5 per cent.
„ 14 „ „ between	5 and 10 per cent.
„ 13 „ „ „	10 „ 15 „
„ 7 „ „ „	15 „ 20 „
„ 3 „ „ „	20 „ 25 „
„ 1 „ „ „	25 „ 30 „
„ 2 „ „ „	35 „ 40 „

The great tendency of the eosinophil count was to decrease from the sixth to the eighteenth month after infection. This was ascertained from such cases as were admitted to hospital. The average eosinophil count was as follows:

In 6 months.	18	per cent.
" 7 "	16.7	"
" 8 "	11.8	"
" 9-12 "	15.7	"
" 12-18 "	11.7	"

These observations fully confirm the previous work of Day (7) on the blood-picture in early bilharziasis amongst the Egyptians.

*Red blood corpuscles.* Taking into account the conditions of active service under which the troops have been living, the average grade of anaemia was extremely slight; the average cell count was 4,660,000, haemoglobin 88 per cent., and colour index 0.95.

*Antibody content of the blood.* In this series of forty-five cases the sera of twenty-five were submitted to the specific complement-fixation test I have recently described for bilharziasis (*Journ. R.A.M.C.*, April, 1919), and twenty, or 80 per cent., gave a completely positive result, while two, or an additional 8 per cent., gave a partially positive one.

*The symptoms of late vesical bilharziasis, the result of repeated hyperinfection.* The late stages of the disease have, fortunately, not been met with so far amongst Australian troops, and one may legitimately express the hope that in these lighter infections they never will be.

In Egypt, the effects of chronic vesical bilharziasis are abundantly manifest in those natives who are constantly at work in the irrigated agricultural districts, where reinfection repeatedly occurs, and it is in these natives that the late and distressing manifestations of the disease are so constantly seen.

Following on the stage of early localized bilharziasis with repeated infection with maturing worms and fresh accumulations of deposited ova, the pathological lesions, and in consequence the clinical symptoms, become more and more pronounced. Such an infiltration of the bladder wall with ova may ensue that actual mechanical obstruction of the *viae naturales* takes place with back-pressure symptoms, a lowered resistance of the tissues, and the establishment of secondary infections. In this way cystitis is produced, with the excretion of alkaline offensive urine, the deposition of phosphates in the form of urinary calculi, and ascending pyelonephritis. Mechanical infiltration of the penis and urethra by ova occurs, producing the most profound anatomical changes in the organs which materially add to the obstruction. Periurethral and perineal abscesses form, and finally, with continued irritation, a malignant growth, either of the bladder itself or of the urethra, may supervene.

The final picture may be that of a chronic septic cystitis with a superadded renal insufficiency, with the excretion of alkaline urine of low specific gravity and diminished urea content, and death from uraemia.

The cause of death in vesical bilharziasis may be due to—

- (a) Sepsis due to septic cystitis and ascending urinary infection.
- (b) Uraemia due to back-pressure atrophy of the kidneys and chronic interstitial nephritis.
- (c) Vesical carcinoma with a tendency to metastatic growths in the myocardium.

In these terminal stages Day has shown that the blood-picture is considerably modified in the relative increase in polymorphonuclear elements and a corresponding decrease in the percentage of eosinophil cells.

I would suggest that, from experimental data in monkeys, the pulmonary tissues must be involved in a high percentage of heavy *B. haematobia*, infections, for, owing to the peculiar habitat of the adult worms in the pelvic venous plexuses, their ova and the worms themselves are specially liable to be filtered out into the capillary branches of the pulmonary artery. The presence of these parasites produces an interstitial pneumonia, the importance of which is obvious.

## (2) *Clinical Picture of Intestinal Bilharziasis Infection with Bilharzia mansoni.*

### *Symptoms of Early Intestinal Bilharziasis.*

The observations detailed below are based on an analysis of thirty-eight cases of infection with *B. mansoni*. Thirty-three of these had a concomitant vesical infection with *B. haematobia* as well.

In four, lateral-spined ova, pathognomonic of *B. mansoni*, only were found in the faeces, but systematic urinary examination was not conducted over a sufficiently long period to exclude the coexistence of a *B. haematobia* infection as well; in only one case could the entire absence of the latter worm be absolutely proved. The vesical manifestations in the cases with mixed infections need not be further dwelt upon. It is, however, to be remarked that thirty out of these thirty-eight first reported sick on account of their vesical, and not on account of any associated intestinal, trouble.

Even on careful cross-examination eleven of these failed to give any history of intestinal symptoms, though lateral-spined ova had been discovered in all of them by a systematic examination of the faeces.

The latency, insidiousness, and symptomless character of the intestinal form requires to be laid stress upon. I am convinced that there is no intestinal affection which, on this account, is more likely to be missed.

In the remaining cases the patients themselves had not attached much significance to such almost trivial intestinal symptoms as they had noted. These were a sense of uneasiness in the rectum, with the appearance of blood and mucus in the stool and occasional attacks of diarrhoea. A few, however, gave a history of such intermittent dysenteric attacks with tenesmus. In the most severe infections, these lasted as long as two or three weeks and were accompanied with considerable emaciation.

In the latent periods, it may be for weeks or months, the only sign of active disease is an occasional looseness of the bowels.

Rarely a history of constantly recurring abdominal pains with painful peristalsis was obtained.

No dyspeptic symptoms were noted.

In the *microscopic examination of the faeces*, beyond the demonstration of the characteristic lateral-spined ova, there is little to note. Preparations should be searched under a low power, and one should by no means rest content with the perfunctory scrutiny of a single specimen; three or more specimens should always be examined. One must remember that in the particular very small amount of faecal matter chosen, no ova may be present, though three or four may be found in the very next preparation.

The outer portion of a solid stool, especially if any tags of rectal mucus are attached, affords the best chances of success. The solid faecal matter or mucus should of course be well triturated with saline. In thirty-eight cases lateral-spined ova alone were found, but in a few cases they were associated with the terminal-spined variety.

*Abdominal palpation* revealed little, save localized and tender points, along the course of the colon: but at no time could one feel the local thickenings or tumour-like polypoid masses which are such common features in the later stages of the disease in Egyptians.

*Digital examination* of the rectum revealed no feature of note.

*Sigmoidoscopy.* Madden (6) reports that the earliest evidence of bilharzial infection of the rectal mucosa is the presence of small, dark-red, coarsely granular patches scattered throughout the paler normal mucosa. In time these granulations increase in size and eventually become papillomata. Later, a more generalized infiltration of the whole bowel wall takes place. The redundant mucosa tends to prolapse at first during the act of defaecation, but later it becomes a permanent protrusion and on top of this the definite slender-stemmed polypi form.

A possible explanation of the focal lesions of intestinal bilharziasis and the latent nature of the infection may be culled from pathological studies, from which it appears that at first the deposition of ova in the submucosa is widely distributed and focal accumulations are not as marked as in the case of *B. haematobia* infections; this is possibly to be accounted for by the smaller egg-laying capacity of *Bilharzia mansoni* as compared with that of the former worm.

*Blood investigation.* As there were so few pure *B. mansoni* infections in this series it is not possible to give any trustworthy statistical records.

In cases of double infections with *B. haematobia* and *B. mansoni*, neither the total leucocyte count nor the red cells differed very materially from that already given for *B. haematobia* alone. The eosinophil count was on the whole rather higher—that is, about 18.6 per cent. This is what one would have expected on theoretical grounds.

*The complement-fixation reaction* on twenty cases of intestinal bilharziasis gave completely positive results in eighteen, or 90 per cent.

*Urine examination.* In thirty-three cases of double infections terminal-spined ova were found, and in six the *lateral-spined* variety were demonstrated as well.

*The later manifestations of intestinal bilharziasis (B. mansoni).* As in the case of the vesical form, these most distressing conditions have not been seen in Australian or British troops.

These late manifestations consist of various complications of the intestinal canal and liver.

(a) Polypoid growths inside the bowel wall, mainly of the colon, which on sloughing give rise to ulceration, often of considerable extent and involving the submucosa.

(b) Pericolitis with formation of subperitoneal tumour-like granulomata.

(c) A periportal cirrhosis, first described by Symmers (8), is especially associated with *B. mansoni*. Although the advanced *pipe-stem* cirrhosis is not commonly met with at autopsy, a finer degree of fibrosis more generally exists.

I have already stressed the fact that in the initial toxæmic stages of bilharziasis the liver is the primary and most constant organ to be involved in both forms of infection, but the more gross changes seem to take place only in the case of *B. mansoni*, for the reason that the worm is specially addicted to the portal system.

(d) Other lesions are due to the deposition of ova in the connective tissues. Such are ischiorectal abscess and fistulae connected with infiltration of the perirectal tissues. Secondary carcinoma supervening on these lesions is uncommon.

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## REFERENCES.

1. Edgar, W. H., 'Yangtze Fever', *Journ. State Med.*, Lond., 1913, xxi. 542.
2. Bassett-Smith, 'Blood Examination in a Case of Katayama Disease', *Brit. Med. Journ.*, 1912, ii. 1208.
3. Miyagawa, Y., 'Beziehung zwischen Schistosomiasis japonica, etc.', *Centrb. f. Bakt., Abt. Orig.*, Jena, lxi. 132-142.
- 3 a. Laning, R. H., 'Schistosomiasis on the Yangtze River, with Report of Cases', *U. S. Nav. Med. Bull.*, 1914, viii. 16, 36.
4. Flu, P. C., 'Beitrag zur Lösung der Frage ob *Sch. mansoni* identisch ist mit *Schistosomum haematobium*', *Centrb. f. Bakt., Abt. Orig.*, Jena, lxi. 389-403.
5. Lawton, F. B., 'Schistosomum mansoni: Early Clinical Features of the Disease', publication by Commonwealth of Australia, Department of Defence, 1917, Part ii.
6. Madden, F. C., *Surgery of the Tropics*, MS. Report, 1919.
7. Day, H. B., 'The Blood Changes in Bilharziasis', *Lancet*, Lond., 1911, ii. 1328-32.
8. Symmers, W. St. C., 'Note on a New Form of Liver Cirrhosis due to the Presence of Ova of *Bilharzia haematobia*', *Journ. Path. and Bact.*, Edinb. and Lond., 1903, ix. 237-9.



## PATCHES OF DEEP PIGMENTATION OF THE ORAL MUCOUS MEMBRANE NOT CONNECTED WITH ADDISON'S DISEASE

By F. PARKES WEBER

PATCHES of blackish pigmentation in the mucous membrane of the cheeks, lips, and mouth proper, are occasionally met with which cannot be attributed to disease of the suprarenal capsules. They are, it has been supposed, sometimes analogous to simple pigment-naevi of the skin. Some of them may be, as Dr. G. Pernet suggests, allied to the black patches which are not uncommon on various parts of the mucous membrane of the mouth in dogs and other animals. In some cases it has been suggested that they are of racial (ethnic) or atavistic origin. In other cases they have been considered to represent a disturbance in the distribution of pigment in the mucous membrane analogous to that which occurs in the skin in freckling (ephelides, lentigines), and they are occasionally associated with circum-oral freckle-like spots on the face. In a few cases it has been claimed that they were causally connected with pernicious anaemia. In some cases they may have been set up by local haemorrhages and inflammatory complications connected with foul teeth and pyorrhoea alveolaris.

A man (M. G.) aged 57 years, a Hungarian Hebrew tailor, was admitted to hospital on March 11, 1916, under my care, suffering from advanced and acute pulmonary tuberculosis and tuberculous spinal caries. He had remarkable, deep (blackish) pigmentation of the buccal mucous membrane and pigmentation, to a less extent, of the mucous membrane of the palate and lips. There was likewise considerable pigmentation of the skin of the face and he was of dark complexion. He did not show the pigmentation typical of Addison's disease elsewhere on his body. He did not know when the pigmentation in his mouth and buccal mucous membrane first appeared—in fact, he seemed to be unaware of its existence until we asked him about it. In the hospital there was considerable pyrexia and progressive loss of weight. The brachial systolic blood-pressure was low, varying from 95 to 105 mm. Hg. A blood-count (March 11, 1916) gave 6,800,000 red cells and 8,125 white cells to the cubic millimetre of blood. The Wassermann reaction was negative. The urine contained a trace of albumin. Examination of the gastric contents after a test breakfast proved the presence of a normal amount of free hydrochloric acid.

The patient died on March 29, 1916, and the *necropsy* showed extensive miliary tuberculosis of both lungs with breaking-down at the apices, tuberculous caries (with abscess-formation) of the mid-dorsal vertebral column. Miliary tubercles were in the liver and spleen. There was likewise a small tuberculous focus in one kidney. No evidence of disease was detected by macroscopic or microscopic examination in the pancreas, pituitary gland, pineal body, or either

suprarenal gland. The solar plexus was not specially examined. In regard to the pathological examination of this case I am much indebted to Dr. H. Schmit.

What the cause was of the pigmentation in the mouth in this case I am at a loss to know. The case was not one of Addison's disease, nor was it one of haemochromatosis. There may perhaps have been a racial or atavistic element in it (see farther on); the patient came from Hungary, and was of Hebrew family. On the whole, I am inclined to regard the pigmentation as analogous to that discussed by Sir Jonathan Hutchinson and Radcliffe Crocker, to which I shall allude farther on.

Certain French observers maintain that there may be a 'physiological' pigmentation of the mucous membranes, occasionally (in Lascars and some Roumanian Jews, for instance) of racial (ethnic) origin (1). Cases of pigmentation of the buccal or oral or both buccal and oral mucous membrane of unknown causation have been demonstrated by H. Dufour and Alardo (2), and by O. Crouzón (3) and others. Milian (4), in Paris, attributed to syphilis the pigmentation of the buccal mucous membrane and lips which he had observed and demonstrated in a syphilitic Roumanian woman, but I am inclined to question whether the pigmentation was really due to the syphilis (see remarks farther on, at the end of this paper).

H. Radcliffe Crocker (5) refers in his text-book to the association of pigmentation of the oral mucous membrane with freckle-like spots on the skin of the lips. In a woman, aged 43 years, under the care of W. Knowsley Sibley (6) for tachycardia, there were spots of deep pigmentation on the skin about the mouth, which had first commenced to appear four years previously. There were similar spots on the mucous membrane of the cheeks and hard palate, but not on the gums. The patient was of dark complexion, much freckled about the face, and in early life she was very liable to bronze on exposure to the sun. Sir Jonathan Hutchinson, when he demonstrated this case (Sibley's patient), said that the pigmentation was of a rare kind, liable to affect persons of dark complexion. He had seen a clergyman, aged 62 years, with a similar pigmentation. Sibley's patient, 22 years later, when she was aged 65, was shown by H. C. Samuel at the Dermatological Section of the Royal Society of Medicine (meeting of January 16, 1919). The pigmentation of the oral mucous membrane was still present, and so was the chronic tachycardia. The heart was slightly enlarged and there was a mitral systolic murmur to be heard.

Sir Jonathan Hutchinson (7) also recorded the case of two girls, who were patients of Dr. J. R. T. Conner. They were twins, brunettes, and quite healthy, and in both of them at the age of 9 years there developed freckling or freckle-like pigment-spots about the mouth—on the lower lip, including the red part (mucous membrane), and (slight pigmentation) on the upper lip. The distribution of the pigmentation in both girls was exactly the same, and it remained unaltered. Dr. Conner has kindly (1919) given me further information regarding these twins. He himself demonstrated them on August 8, 1896, at the Third International Congress of Dermatology, London, 1896 (8). They were first brought to him in

that year, at the age of 12 years, and according to the mother the pigmentation had appeared only three years previously (there seems in this respect to have been an error in Hutchinson's account). From the time when it was first noticed the pigmentation did not vary, excepting that the spots were darker in summer. One of the twins died at the age of 20 years, from intussusception, at the Metropolitan Hospital (London), but the other (B. H.) is still living and is in good health, now (1919) aged 35 years. By the kindness of Dr. Conner I have just seen her. She appears in good health, and the pigmentation is at present not very striking, but perhaps that may be owing to the time of year (commencement of February 1919). The mother is still living. The father, now dead, was a professional rat-catcher. They had nine children, six girls and three boys. None of the other children showed the pigmentation, and there was no history in the family of pigmentation, nor of any admixture of foreign blood.

In this connexion Crocker also refers to a case described by Balzer, Gaucher, and Milian (9), of a woman aged 29 years, in whom pigmentation was present not only round the mouth, but on the eyelids, back of the hands, and forearms; it was first noticed during convalescence from an attack of typhoid fever.

Sir H. D. Rolleston, at the Clinical Section of the Royal Society of Medicine (10), showed a man, aged 25 years, with marked freckle-like pigmentation of the lower half of the face, especially round the mouth. The lower lip presented 'inky' pigmentation towards the angles of the mouth. There were similar patches of pigmentation on the buccal mucous membrane. The patient had not been taking arsenic, but he was thought to be suffering from pernicious anaemia. A subsequent post-mortem examination confirmed the diagnosis of pernicious anaemia and showed that the suprarenal glands were not diseased (11).

At the Dermatological Section of the Royal Society of Medicine, in 1910, Willmott Evans (12) showed a little girl, aged 11 years, with freckle-like spots all round her mouth, and black spots of pigmentation on the buccal mucous membrane, very similar to what was seen in Rolleston's above-mentioned case. The pigmentation, according to the mother, began to appear soon after birth and gradually increased. Evans suggested that the case was an early or mild form of xeroderma pigmentosa, but that diagnosis was not accepted by those who took part in the discussion.

Whether there is any real causal connexion between pernicious anaemia and pigmentation of the buccal and oral mucous membrane is still, I think, unsettled, in spite of T. G. Moorhead's writing on the subject (13). Moorhead's own case was that of a man, aged 28 years, with typical pernicious anaemia. In addition to the uniform lemon-yellow colour of the body there were present a few scattered freckle-like patches of deep brown pigmentation on the face below the eyes and around the angles of the mouth. 'The most striking feature, however, was the pigmentation of the lips and mucous membrane of the inner aspects of the cheeks.' The lower lip on its inner surface was of a bluish, 'inky' colour, and this discoloration was prolonged over the buccal mucous membrane on both

sides, in the form of scattered 'inky' patches, principally on a level with the line of junction of the teeth. The teeth were in an exceedingly foul condition.

Moorhead refers to four other cases of pernicious anaemia showing pigmentation of the buccal mucosa, including Rolleston's above-mentioned case. The earliest one was that described by Hale-White in 1907 (14). His patient was a man aged 22 years, and the diagnosis of pernicious anaemia was confirmed by a subsequent post-mortem examination. Besides the pigmentation of the buccal mucosa there was abnormal pigmentation of the face, trunk, and limbs, partly in the form of small, dark-brown, freckle-like spots, partly in more diffuse brown areas. Another case was recorded by Herbert French in the *Guy's Hospital Reports* for 1909 (15). His patient was a woman aged 33 years, who, in addition to the typical symptoms of pernicious anaemia, showed widespread pigmentation of the skin in patches and specks, pigmentation of the mucous membrane on the inside of the cheeks, and purulent tooth sockets. The diagnosis of pernicious anaemia was also in that case confirmed by a subsequent post-mortem examination. Another case is mentioned by A. Lazarus in Nothnagel's *Encyclopaedia of Practical Medicine* (16). The patient, when seen by him, was suffering from pernicious anaemia, and the tip and back of the tongue and the buccal mucous membrane were the sites of small spots and patches of circumscribed reddish-brown mahogany-like discoloration, which were hyperaesthetic; and Lazarus thought they were probably the result of haemorrhages.

It seems that in some such cases the relation of the pernicious anaemia to the intra-oral pigmentation may have been an *indirectly* causal one, and that the pigmentation may have been set up by local haemorrhages and local inflammatory conditions associated with foul teeth and pyorrhoea alveolaris. In this connexion a case shown by Sir H. D. Rolleston at the Medical Society of London in 1902 (17) may be referred to. The patient was a man aged 40 years, who complained of abdominal pain and constipation. There was a peculiar black pigmentation of the mucous membrane of the lower lip. When the lower lip was turned down, vertical lines of black pigment were seen arranged in the same direction as, but superficial to, the blood-vessels. The pigmentation was strictly limited to that portion of the lower lip opposed to the lower incisor teeth, which were loose, very foul, and coated with much tartar. The patient was a French-polisher by trade, but there was no definite evidence of saturnism, though there was a doubtful 'blue line' (lead line) on the gums. There was no satisfactory evidence in favour of Addison's disease or haemochromatosis.

*In conclusion*, I venture to make the following suggestions: (1) There is a certain group of cases in which pigmentation, not connected with Addison's disease, occurs in the mucous membrane of the mouth. The pigmentation is in the form of blackish spots and patches in the mucous membrane of the lips or cheeks and sometimes of other parts of the mouth. It is associated with pigmentation of the skin of the face, especially about the mouth, and possibly (in one or two cases) of other parts of the body. (2) It occurs in persons of dark complexion, perhaps especially in Roumanian Jews and in certain races such as Lascars. (3) It is of

unknown causation, and seems in some cases to be of a 'physiological' or perhaps of atavistic origin. It may be analogous to the black patches often present in the oral mucous membrane of dogs and other animals. It appears to be allied to simple pigment-naevi of the skin on the one hand and to freckles (ephelides, lentigines) on the other. (4) Jonathan Hutchinson was probably the first to call attention to this class of pigmentation, which perhaps should include various cases published by French authors under the headings, 'physiological pigmentation' and 'racial (ethnic) pigmentation'. (5) It is possible that Milian's case (see p. 405) really belonged to this group, though the patient undoubtedly had syphilis. (6) It is possible that a similar kind of pigmentation may be in some indirect way causally connected with pernicious anaemia.

## REFERENCES.

1. Lortat-Jacob, *Bull. et Mém. Soc. Méd. d. Hôp. de Paris*, 1912, third ser., xxxiii. 896; O. Crouzon, *ibid.*, 1913, xxxvi. 248.
2. Dufour, H., and Alardo, *ibid.*, 1912, xxxiii. 509.
3. Crouzon, O., *ibid.*, 1912, xxxiii. 647.
4. Milian, *ibid.*, 1913, xxxvi. 297.
5. Crocker, *Diseases of the Skin*, third edit., Lond., 1905, 608.
6. Sibley, W. Knowsley, demonstrated by Sir J. Hutchinson, *Clinical Journal*, Lond., 1896, viii. 231.
7. Hutchinson, Sir Jonathan, *Archives of Surgery*, Lond., 1896, vii. 290.
8. Conner, *Third Internat. Congress of Dermatology, held in London, 1896: Official Transactions*, edited by Dr. J. J. Pringle, Lond., 1898, p. 929.
9. Balzer, Gaucher, and Milian, *Annales de Derm. et de Syph.*, Paris, 1897, third series, viii. 1106.
10. Rolleston, H. D., 'Pigmentation of the Circum-oral Skin and of the Buccal Mucosa in Pernicious Anaemia', *Proc. Roy. Soc. Med., Clinical Section*, 1909-10, iii. 9.
11. Rolleston, H. D., 'Sequel to a Case of Pigmentation', *ibid.*, 1909-10, iii. 216.
12. Evans, Willmott, *Proc. Roy. Soc. Med., Dermat. Section*, 1909-10, iii. 57.
13. Moorhead, T. G., 'Pigmentation of the Buccal Mucosa in Pernicious Anaemia', *Brit. Med. Journ.*, 1910, i. 865.
14. Hale-White, W., at the meeting of the Assoc. of Phys. (1907), *Quart. Journ. Med.*, Oxford, 1907-8, i. 108.
15. French, H., *Guy's Hosp. Rep.*, Lond., 1909, lxiii. 103.
16. Lazarus, A., Nothnagel's *Encyclopaedia of Practical Medicine*, Section on Diseases of the Blood, English edition, Philadelphia and Lond., p. 270.
17. Rolleston, H. D., *Trans. Med. Soc. Lond.*, 1902, xxv. 358.
18. Samuel, H. C., 'Case of Pigmentation of the Mucous Membrane', *Proc. Roy. Soc. Med., Dermat. Section*, 1918-19, xii. 27.



## HEART-BLOCK AND BRADYCARDIA FOLLOWING INFLUENZA

By E. A. COCKAYNE

IN cases of simple influenza, and in many with pulmonary complications, bradycardia was extremely common during the epidemic of 1918 and 1919, in which many hundreds of cases were admitted to the Royal Naval Hospital, Haslar. In the majority of cases, after the temperature had become normal, the pulse-rate quickly fell below 60 and remained between 50 and 60 for a variable number of days. In more extreme cases a pulse-rate of 36 to 48 was met with. I took notes of one hundred and thirty-two in which the pulse fell below 50, and most of which came under my own observation at some period of their illness. Polygrams were taken in fifty-five cases by Dr. G. E. S. Ward, who found that in nineteen the bradycardia was due to a condition of partial heart-block. In some of the remaining one hundred and thirteen heart-block may have been present, but was not proved.

The cases of heart-block may be divided into sinus-block, prolongation of the *a-v.* interval, 2:1 and 3:1 heart-block. No case of complete heart-block was met with.

*Sinus-block.* This was present in one case, a boy of 16 with a pulse-rate of 40.

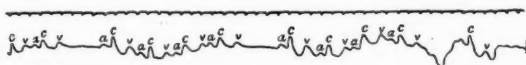


FIG 1.

A.W. E 2. 13 10 18.

Occasional sinus block.

At first an entire cardiac cycle was missed almost every other beat: later, the missed cycles occurred less frequently and less regularly, and the rhythm always became more normal towards the end of the day. The condition gradually disappeared until sinus-block only occurred once every two or three minutes and finally ceased altogether. The total duration of the abnormality was about twenty-eight days. Influenza in this case was complicated by mild pneumonia of the right side.

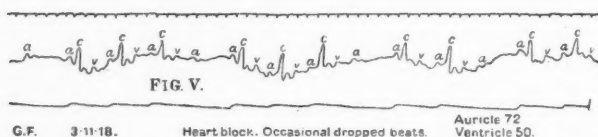
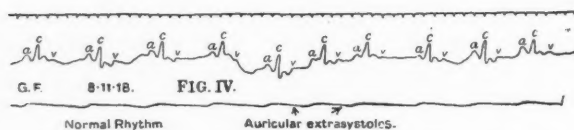
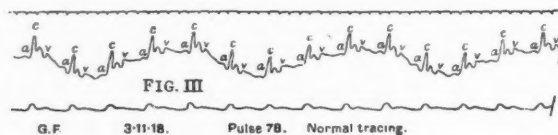
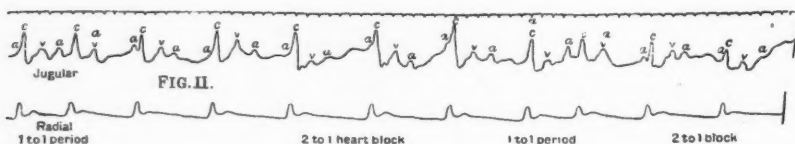
*Prolonged a.-v. interval.* This was present in two men aged 18 and 44 and lasted nine and twenty-two days respectively. The pulse-rate in one varied

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between 40 and 48, and in the other between 38 and 48. Both had mild pneumonia.

*2:1 Heart-block.* This was found in nine cases, one aged 16, one 17, four 18, two 19, and one 36 years of age. The condition lasted in the shortest case one day, and in the longest thirty-three days, the average duration being twelve days. As the heart-block became less complete, intervals of irregular pulse were noted and were due to a mixture of 2:1 and 1:1 rhythm. Six were cases of mild pneumonia, one was fairly severe, and in another a relapse occurred in which heart-block persisted during the pyrexia. In one case the pulse-rate varied



This tracing shows heart-block with missed beats at irregular intervals. The auricle is beating quite regularly at 72. The ventricular rate is about 50. The periods of heart-block and auricular extra-systoles come on in quick succession.

in a remarkable way. One day it was 38 in the morning, 78 in the afternoon, and 36 in the evening. A polygram taken when it was 78 showed a perfectly normal tracing. Later in the same day another showed periods where there were numerous auricular extra-systoles alternating with periods in which there was 2:1 heart-block.

Another man of 18 had bradycardia with a pulse-rate of 48 two months after the disappearance of his heart-block. He had just returned from convalescent leave, so that it is not known whether this was preceded by fever. Unfortunately no polygram could be obtained.

3:1 *Heart-block*. Six cases were met with, three in men aged 18, one 19, and two aged 28 years. The total duration of partial heart-block averaged about fourteen days.

A case of interest was a man aged 52, suffering from mild pneumonia of both lungs. His pulse-rate was 44. A polygram showed that he had auricular fibrillation, probably due to chronic myocardial degeneration. His slow pulse was probably due to heart-block.

The points brought out by these cases are that the majority occurred in young men and that all had pneumonia. The pneumonia in most of them was very mild, and in none really severe. In four cases there was no sputum. In six the sputum was examined and the predominant organism was found in three to be the pneumococcus, in two a haemolytic streptococcus. In the sixth the *Streptococcus mucosus* was abundant in two specimens examined, and the *Micrococcus catarrhalis* was also present. In three others in which the sputum was not examined secondary infection with a streptococcus was suspected from the complications. Most of the cases were examined at a time when a good medium for growing the *Bacillus influenzae* was not available. All the cases were kept in bed until some days after heart-block had disappeared, and when they were examined a month or six weeks later only one complained of any cardiac symptoms (praecordial pain and giddiness). None showed any undue irritability of the heart.

*Simple bradycardia*. It was found impossible to differentiate all these cases from the cases of heart-block by clinical observation. In one proved by polygraph to belong to this group a pulse-rate of 36 was present. On the average, simple bradycardia was of shorter duration, four or five days, but a pulse-rate consistently below 48 was found in five cases lasting twenty-six, seventeen, twelve, eleven, and ten days respectively, in all of which heart-block was excluded by means of the polygraph.

In a man of 18 a remarkable phenomenon was noted. The pulse-rate was 44, the respirations were 44, and the temperature normal. The rapid respiration may be accounted for in part by the fact that he had been gassed seven months before.

As in the cases of heart-block, the majority of cases of simple bradycardia were met with in young men.

39 were aged 18 or under 18 years.

20 " " 19 and 20.

21 " " 21 to 25 inclusive.

21 " " 26 to 30.

12 " " 31 or over.

In almost all of them some involvement of the lung was present. Only in three is it definitely stated that the lungs were normal. In a few there was only bronchitis of the larger tubes, and in others fine râles were heard. The great majority (seventy-nine cases) had a mild attack of pneumonia.

In twelve the pneumonia was fairly severe, but none of the cases were of a really bad type. The sputum was examined in thirty cases. In seven the *Bacillus influenzae* was found, once in pure culture; in eighteen the pneumococcus alone or with other organisms; in eight the streptococcus; in five the *Micrococcus catarrhalis*; in two the *Streptococcus mucosus*. Gram-negative bacilli of two types, Friedlander's pneumo-bacillus and *Staphylococcus pyogenes aureus*, were also met with. In eleven other cases a streptococcal infection was inferred from the complications. One of the cases of pneumonia with *B. influenzae* and pneumococci in the sputum in November had suffered from pneumonia followed by heart-block in July, and had had the *Streptococcus mucosus* in large numbers in the sputum.

Only one examination of the sputum was made in each case, and, as in the cases of heart-block, the majority were done at a time when a good medium for the *B. influenzae* was not available.

Fourteen cases were examined at the beginning of the third rise in the epidemic. The *B. influenzae* was grown from naso-pharyngeal swabs at the first attempt in twelve, in one of which *B. influenzae* and streptococci were also found in the sputum. In one no organism was identified after two swabs, and in another streptococci only were grown. This suggests that *B. influenzae* would have been found in a far higher percentage of cases had this method been used throughout.

It seems probable that heart-block and simple bradycardia are both due to the same toxin. If influenza be due to a filterable virus, as recent work suggests, this virus may elaborate the poison. On the other hand, the frequency with which the *B. influenzae* has been found in the throat and in the less seriously affected part of the lungs at post-mortem examinations shows that, if not the primary cause of the disease, at least it is almost invariably present as a secondary invader, and so may produce this special toxin. In either case it appears certain that an infection of the upper air-passages may cause some degree of bradycardia; but a pulse-rate of less than 50, or partial heart-block, was almost always associated with some involvement of the lung. The severe infection of the lung due to the streptococcus apparently prevents the occurrence of marked bradycardia or heart-block.

Atropin in doses large enough to cause slight poisoning was tried in four cases of heart-block and produced very slight and only temporary increase in the pulse-rate. In two cases of simple bradycardia the increase in pulse-rate was more marked but no more lasting.

Inhalation of amyl nitrite in one case of simple bradycardia, given a day or two before the condition began to clear up, raised the pulse-rate from 48 to 120, but a minute later it was 48 again. In another case in which no polygram was taken it rose from 48 to 56 and quickly fell again.

The acceleration of the heart-beat produced by these drugs does not prove that the bradycardia is due to the vagus, since both are known to quicken the heart after experimental severance of the muscular continuity of the auricle and

ventricle. It is much more probable that the slow pulse is caused by poisoning of the myocardium, especially that of the sino-auricular node.

The cases appear to arise under the same conditions as those of heart-block, which are undoubtedly due to poisoning of the muscle of the auriculo-ventricular bundle. Further evidence is afforded by the two cases of marked bradycardia with prolongation of the *a.-v.* interval, which in itself cannot produce a slow pulse. Such a combination could then be explained by the fact that both the sino-auricular node and also the auriculo-ventricular bundle had been affected by the same toxin.